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**Formation and occurrence of
bis(chloromethyl)ether and its prevention
in the chemical industry**

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Please remember that like any other scientist I hope to present probable and reasonable solutions, not certainties. Yet imperfect as they may be, probable solutions must take precedence over no solutions at all.

Marvin Harris

To the memory of my maternal grandparents Franz and Genovefa Krapf.

Preface

I wish to express my thanks and gratitude to all those who helped in this study:

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* * *

The time schedule of the work done was as follows:

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Perstorp, autumn 1982.

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Abstract

TRAVENIUS SZM. Formation and occurrence of bis(chloromethyl)ether and its prevention in the chemical industry. *Scand j work environ health* 8 (1982) suppl 3, 86 p. Alpha-chlorinated ethers, especially bis(chloromethyl)ether (BCME) and chloromethyl methyl ether (CMME), are direct-acting inhalation carcinogens. It is above all BCME which presents the greatest lung cancer risk. Pure CMME is only slightly carcinogenic, but technical grade CMME contains 1 to 8 % BCME and is thus a dangerous chemical. Both compounds were formerly used as laboratory reagents and industrial chemicals, mainly for chloromethylating purposes and as solvents. After their carcinogenicity was recognized and confirmed, their use was prohibited worldwide. BCME can be formed in gaseous and liquid phases from its precursors, formaldehyde and chloride ions. This reaction requires a very low pH and/or a very low content of water. Formaldehyde and chloride ions (especially hydrochloric acid) are very common chemicals and, as such, can often occur simultaneously both in industrial processing liquors, residues and effluents and in workroom atmospheres. In the air of industrial operations which use formaldehyde or substances from which formaldehyde is formed and/or released, together with chloride ions or substances from which these ions are formed and/or released, BCME was analytically discovered in concentrations ranging from 0.1 to 10 ppb. The majority of these instances were observed in the textile industry, which uses the "permanent press" process to impart crease and wrinkle resistance to cellulosic fibers. The industries which manufacture, handle, process, and use formaldehyde-based resins, such as urea/formaldehyde, melamine/formaldehyde, and phenol/formaldehyde resins, were suspected of BCME release or its atmospheric formation because the said resins contain free formaldehyde and because chloride ions are often used as catalysts and fire-protecting additives. For this reason, the present research project was carried out, with the following targets: (i) to determine whether BCME is formed when the aforementioned resins are manufactured, handled, processed, and used, (ii) to ascertain how BCME in air can be destroyed, and (iii) to learn more about the modalities of BCME formation from formaldehyde and chloride ions, especially in the atmosphere. The results can be summed up as follows: (i) no BCME was found in experiments which – with the help of special experimental design and equipment – simulated the conditions under which formaldehyde-based resins are manufactured, handled, processed, and used, (ii) on the conjecture that the probable reason for the absence of BCME was the evolution of condensing water vapor, the BCME mopping-up effect of condensing water vapor was confirmed in specially designed experiments, and (iii) as regards the modalities of BCME formation from its precursors in air, it was found that BCME, being a highly reactive substance, exhibits a marked surface effect in confined spaces, a finding which might help explain the uncontrollable variations of BCME concentrations both in laboratory reactors and in industrial workrooms. Furthermore, there are reasons to suppose that the usual methods of collecting BCME from the air by adsorption for analytical purposes are unreliable as the coadsorbed water can destroy BCME in situ prior to the actual analysis, performed preferably by gas chromatography-mass spectroscopy, if the delay between collection and analysis is too long. It was concluded that laboratory simulation experiments aiming to determine how much BCME can be formed from certain concentrations of formaldehyde and chloride ions are unreliable because they do not consider the effect of the reactor volume, the reactor surface area, the reactor surface reactivity, as well as the effect of mass transport phenomena from the air volume bulk to the walls. It was pointed out that the present threshold limit value of one part per billion for BCME might not be quite safe. Calculations showed that the probable carcinogenic concentrations for workers in the chemical industry that used BCME and CMME may have been between 10 and 800 ppb (more often between 10 and 100 ppb). If these figures are compared with values of 0.1 to 10 ppb, ie, the BCME concentrations that can form from formaldehyde and chloride ions in air, it can be seen that there is no sufficient margin of safety. In order to assess the industrial and environmental risks of a possible BCME formation in air more correctly, empirical equations ought to be derived which can be used for calculating the potential BCME concentrations in the atmosphere of the workrooms on the basis of seven variables, namely, the concentrations of formaldehyde, chloride ions and water vapor, the temperature, the volume of the space in question, the area of the surfaces which are in contact with the BCME-containing air, and the mass transfer factor.

Key terms: chloride ions, chloroethers, chloromethyl methyl ether, direct-acting carcinogens, formaldehyde, formaldehyde-based resins, lung cancer, melamine/formaldehyde resins, phenol/formaldehyde resins, urea/formaldehyde resins.

Introduction

At the beginning of the 1970s, it was discovered that bis(chloromethyl)ether (BCME) and chloromethyl methyl ether (CMME), which were used as reactants in the chemical industry, were dangerous carcinogens.

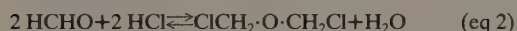
The use of these substances was then subjected to special regulations, and, if they are used at all at present, hermetically closed and remotely controlled equipment must be designed and built to ensure their safe handling.

Later, it was found that CMME owes its carcinogenicity, above all, to the admixture of BCME in the technical grade CMME.

CMME decomposes by the action of water to methanol, formaldehyde and hydrogen chloride:



and formaldehyde can then react with hydrogen chloride to form BCME:



Thus it is BCME that requires special attention.

While the use of BCME and CMME as reactants presents no more problems, as it has become very restricted and as special maximum-safety equipment has been designed to cope with these compounds, there is another danger connected with BCME in industry, namely, that it can be formed in both the gaseous and liquid phase from its precursors formaldehyde and chloride ions.

The latter compounds belong to the most commonly used chemicals in industry. In highly developed countries, the annual per capita consumption of formaldehyde can reach 5 to 20 kg, and the consumption of hydrochloric acid is even higher.

In the manufacture of many industrial articles, formaldehyde, as well as substances forming or releasing formaldehyde, can come together with chloride ions or substances that form or release chloride ions.

Even when formaldehyde and chloride ions are used separately in industrial processes, they can meet and react with each other in the atmosphere if they happen to be released into the workroom air at the same time. Besides, the general atmosphere, especially the polluted air of industrial regions,

may contain both compounds released into the atmosphere by different sources. Thus there can be danger of BCME formation in both industrial and polluted urban atmospheres.

Rough calculations show that the concentrations of BCME that caused the 70 or so documented cases of bronchial cancer may have varied between about 10 and 800 ppb in the workroom atmosphere.

On the other hand, BCME concentrations of up to about 10 ppb (sometimes even more) were measured in the air of industrial operations simultaneously using formaldehyde and chloride ions (especially in the textile industry).

Thus it can be seen that there is reason for concern as regards those industrial situations in which formaldehyde and chloride ions are used or released at the same time and can react with each other.

The most important use of formaldehyde is in the manufacture of formaldehyde-based resins, eg, the urea/formaldehyde, phenol/formaldehyde, and melamine/formaldehyde types.

The unreacted free formaldehyde which is always present in these resins can come in contact with chloride ions if the latter are used in the form of chlorides as (i) catalysts in the manufacture of resins or (ii) additives in the articles made from these resins. The most typical case of an additive is the use of chlorides in particleboards (chipboards) bonded with formaldehyde-based resins (usually urea/formaldehyde resins) in order to achieve a higher degree of fire protection.

As the formaldehyde-based resins are important industrial articles and as their manufacture, processing, handling, and use can create conditions under which the formation of BCME may be suspected, it was decided to use them for the present study.

Thus the purpose of the present project was to ascertain whether BCME is formed and can be determined when formaldehyde-based resins are produced, handled, processed, and used.

As BCME is a direct-acting carcinogen with the atmosphere as a carrier and with the lungs as the target organ, it was looked for analytically only in the air. In actual industrial practice, gaseous BCME can be ex-

pected to be formed and/or occur, above all, either in the headspaces of the process equipment or in the workroom atmosphere.

The experimental work was planned to comprise:

- 1 investigations concerning the formation of BCME in air from formaldehyde and chloride ions;
- 2 investigations concerning the formation of BCME when formaldehyde-based resins are brought in contact with chlorine-containing substances;
- 3 investigations concerning the formation of BCME when formaldehyde-based resins that involve chlorine-containing substances are dried;
- 4 investigations concerning the formation of BCME when formaldehyde-based resins that involve chlorine-containing substances are cured.

In the actual experimental work, stages 3 and 4 were combined and a new stage was introduced, namely, experiments regarding the destruction of BCME in the gaseous phase.

Haloethers in general

In the planning stage, it was intended to investigate the following haloethers:

- a BCME
bis(chloromethyl)ether
 $\text{Cl}\cdot\text{CH}_2\cdot\text{O}\cdot\text{CH}_2\cdot\text{Cl}$,
- b CMME
chloromethyl methyl ether
 $\text{CH}_3\cdot\text{O}\cdot\text{CH}_2\cdot\text{Cl}$,
- c BBME
bis(bromomethyl)ether
 $\text{Br}\cdot\text{CH}_2\cdot\text{O}\cdot\text{CH}_2\cdot\text{Br}$,
- d BMME
bromomethyl methyl ether
 $\text{CH}_3\cdot\text{O}\cdot\text{CH}_2\cdot\text{Br}$,
- e BCEE
bis(2-chloroethyl)ether
 $\text{Cl}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{O}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{Cl}$,
- f BCiPE
bis(2-chloroisopropyl)ether
 $\text{Cl}\cdot\text{CH}_2\cdot\underset{\text{H}_3\text{C}}{\underset{|}{\text{CH}}}\cdot\text{O}\cdot\underset{\text{CH}_3}{\underset{|}{\text{CH}}}\cdot\text{CH}_2\cdot\text{Cl}$.

The literature study and preliminary experiments have, however, shown that haloethers c and d are immediately decomposed by water and water vapor and that haloethers e and f are not formed under the

conditions being investigated. Haloether b was looked for in several experiments involving methanol but was not found in them. Thus the investigations were restricted to the most important and most carcinogenic haloether a, ie, BCME.

Haloethers e, f, and some others are of importance as industrial chemicals and river pollutants (43, 57, 73, 81, 124, 127, 130, 148, 150, 171, 186, 187, 232, 292, 293, 295, 296, 343, 389).

The importance of haloether b (CMME) lies in the following facts: (i) CMME can decompose to its precursors methanol, hydrogen chloride, and formaldehyde, of which the latter two can recombine and form BCME, and (ii) technical grade CMME contains 1 to 8 % BCME as an impurity. Thus, although CMME is only slightly carcinogenic in its own right, it is the BCME content that is mainly responsible for the total carcinogenic effect of CMME.

In the preparation of the present project information was collected concerning mainly the following topics: (i) haloethers and their properties in general, (ii) methods of analysis for BCME and CMME, (iii) the formation of BCME, (iv) the occurrence of BCME under industrial conditions, and (v) the mutagenicity and carcinogenicity of BCME and CMME.

Contact was made with 35 research institutes, industrial corporations, and individual researchers, of which 22 provided information. In a private communication of 30 November 1978 GJ van Esch from the Laboratory for Toxicology, Rijksinstituut voor de Volksgezondheid in Bilthoven, The Netherlands, answered that they could not give any information as the data collection in their institute was governmental property.

Bis(chloromethyl)ether

BCME is also known under the following names: symmetrical (sym) dichlorodimethyl ether, chloro(chloromethoxy)methane (approved by the International Union of Chemistry), alpha, alpha'-dichlorodimethyl ether, 1,1'-dichlorodimethyl ether, and methylchlorex (M-chlorex).

BCME is formed when formaldehyde reacts with chloride ions in an acidic medium:



Several routes of synthesis have been described (58, 122).

In the First World War BCME was tried out as poison gas, together with bis(bromomethyl)ether (BBME), but without great effect (181, 182, 347, 348).

At present, BCME is used mainly for chloromethylations, especially when a combination of formaldehyde and hydrogen chloride is not effective enough, eg, in the case of aromatic compounds and anilides (117).

Reactions between hydrogen halogenides and formaldehyde and between hydrogen halogenides, formaldehyde, and alcohols have been known for a long time, and some of them (besides those for preparing BCME and CMME) are of practical importance, eg, for the preparation of chloromethyl ethers of higher fatty alcohols (316, 317).

BCME has been the subject of many investigations. For example, Böhme (37) investigated the effect of oxygen and sulfur atoms in the alpha-position on the rate of hydrolysis of the halogen-carbon bond. Makridin et al (170) studied the nuclear quadrupole resonance spectra in the antimony pentachloride-BCME complexes. Nichols & Merritt (205) investigated the relative solvolytic reactivities of CMME and BCME, and Gorrie et al (112) made a nuclear magnetic resonance investigation of formaldehyde addition and oligometric equilibria in the formaldehyde/water/acetic acid/hydrogen chloride system.

Olah & Yu (219) proved that chloromethyl alcohol ($\text{Cl}\cdot\text{CH}_2\text{OH}$) was an intermediate in chloromethylations, while Tou et al (285) studied the hydrolysis of BCME under acidic, neutral, and alkaline conditions. The molecular conformation of BCME was studied by Charles et al (47) and by Astrup & Aomar (13).

A good coverage of BCME and other haloethers as far as reactions and uses are concerned can be found in Beilstein (38, 228, 240, 241, 242).

The following investigations concerning or involving BCME and other haloethers were made during the last 20 a: production of dihalogenated ethers of the type $\text{Cl}\cdot\text{CH}_2\cdot\text{O}\cdot(\text{CH}_2)_n\cdot\text{O}\cdot\text{CH}_2\text{Cl}$ by Allen & Allan (5); reactions of BCME with alpha-acetothienone to obtain thiophenes by Belen'kij et al (27); reactions of BCME with olefins, allenes, divinylacetylene hydrocarbons, 1,3-diene hydrocarbons, alkyl and allyl

halides by the Armenian school of Gevorkyan (99, 100, 101, 102, 103, 104, 280); production of improved elastomeric materials by Johncock & Hewins (139); Reformatsky reactions by Johnson & Zitsman (140, 342); and various condensation reactions by the Roumanian school of Iovu (131, 132, 133, 134, 135, 136), and by Nikolaev et al (206, 207) and Novgorodov et al (214, 215).

Olah et al (218) studied the chloromethylation of benzenes and Szymik et al (272) prepared a polycondensation resin using a bischloromethylated thioether. Taylor & McLaughlin (273) prepared several quaternary salts of BCME intended as formaldehyde donors, while the German rayon research has been interested in polyhalogenated compounds (341).

Fishbein (83) listed the following four principal uses for BCME and CMME as industrial reactants: (i) the preparation of ion-exchange resins, (ii) the formation of water-repellents and other textile treating agents, (iii) the manufacture of polymers, and (iv) solvents for polymerization reactions.

At the end of the 1960s BCME and CMME became an important occupational health issue in the United States, and complaints were directed against the industry using these haloethers (114, 234). Charges were made against the manufacturers for trying to obfuscate the issue (24, 25, 44, 106, 166, 269, 366, 367).

Although the uses of the carcinogenic haloethers BCME and CMME have become greatly restricted in the chemical industry, these reagents could not be replaced by less dangerous compounds in some chemical processes. For this reason, they are still used for difficult chloromethylations, but hermetically closed and specially isolated equipment was built to handle them (116, 123, 238).

Properties

BCME has a molecular weight of 114.96, a density of $1.33\text{ g}\cdot\text{cm}^{-3}$, and a boiling point of 105°C (12, 118, 149, 294). The stability of BCME and CMME in water is very low. The reaction half-time of the decomposition of BCME is 10 to 40 s. On the other hand, the gaseous phase of BCME is relatively stable even in humid air. Water in the liquid phase effectively prevents the formation of BCME from its precursors.

Nonpolar liquids (n-pentane, n-hexane, dichloromethane, etc) do not decompose

BCME and can thus be used as solvents for BCME, eg, for calibrating purposes. The BCME concentration (even if it is a very low one) in dichloromethane remains constant for several months.

BCME does not decompose in extremely acidic liquids. On the other hand, alkalis of all sorts will decompose BCME very quickly in the liquid and gaseous phases.

The conditions for preventing the decomposition of BCME in liquid media are: (i) use of as little water as possible and (ii) as low a pH value as possible.

Chlorides (which are catalysts for BCME formation from its precursors) help prevent the decomposition of BCME in aqueous media.

BCME is a strong irritant of the eyes (danger of keratitis) and of the respiratory organs. Its acute effect on the organism is attributed to its combination with the thiol groups in proteins, particularly enzymes.

Drew et al (66) found the following LC₅₀ values (lethal concentrations with 50 % mortality) for exposures of 5 h/d for 14 d in air as regards acute inhalation toxicity: 55 and 65 ppm of CMME and 7 and 7 ppm of BCME for rats and hamsters, respectively.

Bettink (34) mentioned that the vapor pressure of BCME at 20°C is equivalent to a concentration of 180 ppm in air. A concentration of 3 ppm of BCME in air irritates eyes and mucous membranes, and even a concentration which did not reach the threshold of perception is reported to have caused severe eye damage after exposure of several hours' duration (severe conjunctivitis with keratitis punctata). These manifestations occurred several hours after the contact with BCME had stopped. A concentration of 100 ppm – if inhaled – can kill the exposed person within minutes. The highest tolerable concentration in air has been given as 5 ppm for both BCME and CMME.

BCME has caused deaths from pulmonary edema in dogs and cats (270).

Even as regards the upper respiratory tract, it was pointed out by Leong et al (160) that both BCME and CMME present a health risk at such low concentrations in air that there is no irritation to serve as a warning to the exposed persons.

Thus BCME can be regarded as an extremely toxic substance. But when Collier referred to BCME in this way (51), she was corrected by Van Duuren et al (309) who said that such a statement was “misleading”

and that BCME was better referred to as a “potent lung carcinogen” in order to stress where the greatest moment of danger lies.

Analytical chemistry

According to Yao & Miller (337) and Yao & Zollinger (338), there are conceivably six methods for BCME analyses, namely:

a direct gas chromatography (not suitable for detecting part-per-billion levels);

b on-column concentration gas chromatography, eg, the patented Rohm & Haas procedure (91, 334) or the Williams & Umstead method (336);

c adsorber gas chromatography, with thermal flashing-off of the adsorbate into the gas chromatographic column, eg, according to Parkes et al (223);

d adsorber mass spectrometry, capable of detecting 0.1 ppb levels of BCME, like Collier's procedure (51) or the Varian Associates' procedure in the portable version (75);

e adsorber gas chromatography – mass spectrometry with very high specificity and selectivity, which was successfully used by Yao & Miller (337), Shadoff et al (259), Evans et al (76), Sawicki (248), Choudhary & Cooper (49), Ellgehausen (70), and Berkley et al (29) and as the official method of the US National Institute for Occupational Safety and Health (NIOSH) (195); besides, it is recommended for “priority pollutants” by Ottmers et al (222); according to the private communication of 17 August 1978 from D Ellgehausen it is possible to increase the selectivity of the procedure with the use of a gas chromatographic separation step before the actual analysis.

f derivatization, eg, with the sodium salt of 2,4,6-trichlorophenate (143, 196, 249, 266), possibly as a rapid monitoring method developed by the Dow Chemical Co (19, 62, 63, 64, 142, 264, 265, 365) or with the modified target compound (337, 338), other derivatization methods being the one according to van der Ven & Venema (312, 313) and the one according to Baba & Tanaka (20).

Furthermore, there are two other possibilities for BCME analysis, namely:

- g gas-liquid-solid chromatography, studied by the Bertoni-Bruner team (30, 45);
- h straight gas chromatography – mass spectrometry without enrichment, suitable for dynamic laboratory experiments.

Adsorption procedures are more sensitive than methods without enrichment. Collier (51) obtained a sensitivity of less than 0.1 ppb with a 15,000-fold concentration on Porapak Q, and Evans et al (76) obtained a sensitivity of 0.01 ppb of BCME when using 10-l air samples.

There are several substances that can be mistaken for BCME, eg, 1-chloro-2-propanol (a degradation product of polyurethane foam) (253) and there are also several $m/e=79$ ions which, however, do not meet the other requirements for BCME, eg:

CH_4SiCl , CH_3S_2 , CH_2ClF , $\text{CH}_4\text{O}_2\text{P}$, $\text{C}_5\text{H}_5\text{N}$ and C_6H_7 .

Three requirements must be fulfilled if BCME is to be correctly identified (49, 259): (i) the mass of the molecular fragment must be correct, (ii) the retention time must be correct, and (iii) the observed chlorine isotope ratio must be correct.

A comparison regarding the sensitivities of the various analytical methods for BCME was made by Müller et al (189). Research and industrial laboratories rarely have experience with two or more methods. They usually develop only the approach to a given analytical problem that best suits their requirements as far as a certain compound is concerned. However, there seems to be an agreement among most researchers in the BCME field that analytical methods based on the use of gas chromatograph – mass spectroscopy combinations have so far been the most satisfactory.

If BCME has to be determined in the liquid phase, there are several colorimetric methods available (188, 189, 210, 211, 229, 251, 254).

Destruction

It is sometimes of great importance to destroy BCME in the gaseous phase (eg, in the workroom air) and in the liquid phase (eg, in reaction or process liquors).

As already pointed out, BCME is decomposed by water. However, it was found that for liquidating BCME an injection of water

into the reaction vessel containing anhydrous chemicals or chemicals with only a very small amount of water was not adequate. The reason is that the low solubility of BCME in water can cause only a retarded decomposition of this substance. The rate of hydrolysis is, however, greater in homogeneous media which contain water and in which BCME dissolves. A successful medium of this kind is, eg, a methanol/water mixture.

A very good way of liquidating BCME is to inject ammonia in an aqueous or methanol solution, a procedure which leads to the decomposition of BCME and to a sequestration of formaldehyde as hexamethylene tetramine. In this way, no reformation of BCME is possible because one BCME precursor is missing.

In the present project a mixture of sodium hydroxide and aqueous ammonia was used, with or without an addition of methanol, for killing BCME residues in reactors.

The strong alkali (sodium hydroxide) in the last-named mixture was intended to neutralize the strong acids present in the reactors in some of the experiments. The reactor contents were thus not only neutralized but made strongly alkaline, and the danger of BCME formation was eliminated.

In industry, it is sometimes important to remove BCME from reaction mixtures, from reactor headspaces, and from workroom atmospheres. The following two procedures have been suggested:

- a For the removal of BCME from chloroacetyl chloride (CAC) which is prepared by a photochemical oxidation of vinylidene chloride according to US patent 3,674,664, the CAC containing 100 to 250 ppm of BCME as an impurity is brought in contact with hydrochloric acid at 30 to 160°C in the presence of a Lewis acid or a strong protic acid as a catalyst. Aluminium chloride and oleum are suggested, and the contact time is about 1 h. The BCME content is reduced by this treatment to about 0.3 ppm (59).
- b For the removal of BCME from laboratory or workroom atmospheres the use of silica gel and/or activated alumina is recommended. The adsorption is carried out at a temperature that results in a hydrolytic decomposition of BCME (or, for that matter, of CMME). Temperatures of up to 170°C are named (36).

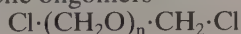
Sources

There are three possible sources of BCME in air: (i) BCME escaping from manufacturing or laboratory equipment into the workroom air when it is being used as a reactant (eg, in an organic synthesis), (ii) BCME escaping from manufacturing or laboratory equipment into the workroom air when formaldehyde or chemicals forming or releasing formaldehyde are used together with chloride ions or chemicals forming or releasing chloride ions or when these chemicals combine in air to form BCME "in the background," and (iii) BCME formed in the general atmosphere which contains formaldehyde and chloride ions released by different sources.

Source i is no more of practical interest because chemical engineering techniques can be used to design and build equipment which will not release BCME into the ambient air. Thus it is only source ii that is of interest with respect to industry, while source iii is of importance for the general atmosphere.

Industrial sources. The first type of industry that seriously studied the possible formation of BCME from formaldehyde and chloride ions, in both the liquid and gas phase, was the textile industry, which uses large amounts of formaldehyde-based resins for shrink- and creaseproof treatments of cotton and cellulosic fiber textiles. For example, in the middle of the 1970s, the annual US consumption of urea/formaldehyde and melamine/formaldehyde resins for durable press treatment was about 17,000 t. According to estimates, about 60 % of all cotton and rayon fabrics made in the United States at that time were resin-treated for durable press (which conferred shrink and crease resistance). For another 20 % of these fabrics, formaldehyde in some form was used (eg, in combination with starch in order to stiffen tricot for cutting).

The most important contribution to the BCME problem in the textile industry came from Zollinger and his team in Zürich (344, 345). They found that thermosetting emulsion polymers for nonwoven bonding and the pad-dry-cure cross-linking of cellulosic fiber fabrics are potential BCME sources. In investigations involving the formaldehyde/hydrogen chloride/water/acetic acid system, they showed that BCME and its higher oxymethylene oligomers



can be formed in concentrations of up to 16 mol-%. It was not possible to determine separately the percentages of the various oligo(oxymethylene)dichlorides, as well as the possible carcinogenicity of the individual members of this group of compounds.

In analogy with the situation for oligo(oxymethylene)diacetates it was argued that about two-thirds of the total amount of oligo(oxymethylene)dichlorides might be the member with $n=1$, ie, BCME.

The systems involving formaldehyde, hydrochloric acid, water, and acetic acid were recommended in 1960 by Reeves et al (237) as form D (=dry, on account of the small amount of water used) or form W (with more water). The difference between forms D and W is that the former contains much acetic acid. It is this form D which is dangerous on account of the high concentration of BCME that can be produced.

In 1977, Luther (169) declared that the form D process had never been used commercially. This is a surprising statement because the process in question was very efficient and inexpensive and, at the time it was introduced, nobody knew anything about a possible BCME risk.

Zollinger (345) was the first to recognize that the BCME problem in textile finishing was a serious one, and he underlined the danger in that the results obtained by some authors – namely, that no measurable concentrations of BCME (ie, < 1 ppb) were found in investigations under pad-dry-cure conditions – might be generalized for all types of applications. He insisted that it was necessary to investigate the BCME formation in all new processes involving formaldehyde and chloride ions.

He also pronounced the following warning, which ought to be generally heeded:

In our opinion it is hardly consistent with a responsible publication policy to publish isolated results which demonstrate that harmful (toxic) compounds are not formed under very specific conditions, as the reader may get the impression that this also applies to very similar systems which may not be the case [p 97/33].

As already mentioned, Reeves et al (237) investigated the formaldehyde/hydrogen chloride/water/acetic acid system (in some cases with an addition of acetanhydride), while, at the same time, Tesoro (276) studied the use of bis-pyridinium salts of bis(chloromethyl)ethers of aliphatic glycols for the same purpose, ie, cross-linking of cellulose

Table 1. Formation of bis(chloromethyl)ether (BCME) from a thermosetting acrylic resin.

Catalyst	BCME evolved in drying and curing (ppm)	BCME content in stack gases ^a (ppb)
None	0.40	0.54
1 % of ammonium chloride	1.74	2.35
1 % of ammonium nitrate	0.48	0.65

^a The BCME concentration in the stack gases was calculated from the amount of BCME evolved during drying and curing, according to a formula developed for this purpose.

fibers. The respective bis- and poly(chloromethyl)ethers were prepared from glycols, formaldehyde, and hydrochloric acid at low temperatures and then purified by vacuum distillation.

Ulrich (298) described the efforts to develop effective cross-linking procedures for cellulosic fibers. Besides BCME, the following dangerous compounds were used: methylene disulfate, dichlorodimethyl sulfate, sulfur mustard, and bis-(dichloroethyl)methyl-N.

At the time (before 1960), little was known about many carcinogenic compounds, and this explains the rather terrifying use of chemicals of high carcinogenic potential in this research.

Hurwitz experimented in 1974 with acrylic polymers in the presence of cellulosic-fiber nonwoven webs and found that, if no web was present, the drying and curing of the respective emulsion polymer gave 0.4 ppm of BCME in the near air and 0.54 ppb of BCME in the stack. When ammonium chloride was used, the development of BCME was enhanced (see table 1). Generally speaking, micrograms of BCME evolved from grams of the respective emulsion polymer, which corresponds to about 0.01 mol-% of BCME if the free formaldehyde content is in the low percentage range (125).

Probably the most important document regarding the quantitative data of BCME formation from formaldehyde and chloride ions in air is the NIOSH Burlington report (371). It was deemed necessary to take BCME samples from the air of the textile finishing plants because resins of high free formaldehyde content (carbamates), together with magnesium chloride catalysts, were used.

The carbamates (2 to 7 % of free formaldehyde) give the finished fabric a softer hand and make the fabric more durable than glyoxal resins, which, however, are low in free formaldehyde content (usually less than 1 %). Of the catalysts used (zinc or magnesium chloride) magnesium chloride was thought to be more conducive to BCME formation.

The following conclusions were drawn: Selective sampling of four Burlington Industries finishing plants confirmed the presence of BCME in the textile finishing area. BCME was found both in area samples and in some personal, breathing zone, samples collected in the starch room and padding areas, around the tenter frames, and in the exhaust stacks leading from the tenter frames.

The findings were considered significant although only about one-tenth of the samples in which BCME was thought to exist were found to be positive. In the past, resins of higher free formaldehyde content had been in prevalent use, and it was thought that these resins – when applied in combination with magnesium chloride catalysts – might conceivably have given rise to higher concentrations of BCME. The measured concentrations of BCME were in the parts-per-billion order of magnitude, namely, from 0.4 to about 8.0 ppb.

From the point of view of what is known today, the following remarks must be made: The sampling was done by drawing air through tubes filled with Porapak Q; whereafter the tubes were sent for analysis, either to the Rohm & Haas Co in Philadelphia, PA, to be analyzed by the gas chromatography – mass spectroscopy with a resolution of 0.1 ppb of BCME in air, as described by Col-

lier (51), or to the Dow Chemical Analytical Laboratory in Midland, MI, to be analyzed by means of the gas chromatography – mass spectroscopy magnetic separation and by their new proprietary technique. There was an unavoidable time lag of several days between the collection and eventual analysis. Thus it is strongly suspected that much of the collected BCME was decomposed in situ, inside the collection tubes, by coadsorbed water vapor.

Of particular relevance in this respect is the work done by Berkley et al (29) from 1977, in which it was shown that BCME adsorbed on Tenax GC (a recrystallized 2,6-diphenyl-p-phenylene oxide polymer) from air with a high relative humidity is liable to decompose in the adsorbed state in such a way that, within 24 h after collection, half of the adsorbed BCME amount disappears and, after a week, only a trace of it can be determined.

If something similar happened with the Burlington samples, then it is probable that the nine-tenths of the samples which were expected to contain measurable amounts of BCME turned out to be what can best be referred to as false negatives.

Similarly, in the cases in which measurable amounts of BCME were found, the original concentrations of BCME could have been higher, even much higher, because textile finishing mill atmospheres are environments with high relative humidities of the air.

In some places, there was awareness of the possible effect of coadsorbed water in solid adsorbents in BCME analyses. Methods for BCME analysis developed by two Swiss chemical concerns used a blowing-out of the collection tubes with an inert gas (helium, nitrogen) in order to remove the adsorbed water vapor (50, 69).

On the other hand, Janák et al (138) found that the humidity content of the air had no effect on the results of analyses when water-insensitive compounds were adsorbed on Tenax GC.

The American BCME researcher Marceleno also felt that BCME could be more prevalent in the textile industry than shown by the current analyses because sampling procedures might be only 10 to 15 % efficient in detecting the carcinogen (372).

The whole debate as regards the formation of BCME in textile finishing had positive results. Improvements were made which were characterized by (i) the development and use

of finishing resins with a considerably lowered free formaldehyde content and (ii) the development and use of new catalysts which contain no chloride and sometimes even no metals and are based, instead, on either organic or inorganic acids (213, 299).

Also, the study of the reaction mechanism and kinetics in the formation of BCME received an incentive (174, 337).

The occurrence of BCME in the plastics industry was also investigated. Eisner reported that in January 1973 concentrations of 1.3 to 1.9 ppb of BCME were measured in the vicinity of the reactors used for condensing phenol and formaldehyde at the American firm of Diamond Shamrock Corporation. Two months later the measurements were repeated. Two of the four collected samples exhibited interferences which prevented the detection of BCME. The third sample contained less than 1 ppb of BCME, while 15.5 ppb of BCME was found in the fourth sample. The air concentrations of formaldehyde and chloride ions were however not determined in connection with these measurements of BCME (67).

In Great Britain, the Imperial Chemical Industries (ICI) Ltd also did research on the formation possibilities of BCME, even before the general announcement by Rohm & Haas in December 1972, as regards the atmospheric formation of BCME from formaldehyde and chloride ions. According to a private communication of 11 November 1978 from JS Gardiner there were two principal aims in this work, namely,

- a to devise a reliable, specific, and highly sensitive analytical method for the detection and estimation of BCME (the gas chromatography – mass spectroscopy system was resorted to), and
- b to carry out checks on plants and processes in the ICI's Organics Division, where there was a possibility of a simultaneous presence of formaldehyde and chloride ions. On the whole, about 30 processes and plant situations were examined. The depth of investigations varied considerably, from single checks on several batches of final product to detailed samplings at many stages of a manufacturing process.

The results were as follows: In the atmosphere, the BCME levels did not exceed 1 ppb for concentrations of hydrogen chloride and formaldehyde below 20 ppm. In the

aqueous phase, BCME was not detected (less than 1 ppb) in many water-containing systems and in the respective headspaces when chloride ions and formaldehyde were present in concentrations of up to several percent. Virtually all the 30 or so processes studied involved aqueous reactions, and in these no BCME was detected (detection limit 1 ppb). The nature of these manufacturing processes was, however, not disclosed (126).

Davies reported the contents of the original Rohm & Haas release from 1972 as follows (55): The reaction between formaldehyde and hydrogen chloride proceeds very rapidly at room temperature and 40 % relative humidity, and equilibrium is reached in less than 1 min to yield parts-per-billion levels of BCME for parts-per-million levels of the reactants. The rate and extent of the BCME formation depend on the humidity and temperature. At high humidities, the rate of formation is faster, and, at lower temperatures, the equilibrium concentration is higher. The formation of BCME is rapid in both aqueous and nonaqueous media.

Later, Rohm & Haas and the Dow Chemical Co agreed that the BCME formation was not detectable, ie, it was below 0.5 ppb, if formaldehyde and hydrogen chloride were present at their threshold limit concentrations and at room temperature.

Standish (268) referred to the investigations allegedly made by the US Food and Drug Administration and said to have established that – when clothes treated with a formaldehyde resin to provide a permanent press finish were wetted with methyl chloride and then ironed – the resin and the solvent reacted to form BCME. A number of dry-cleaning workers were said to have been affected. He also said that it had been shown that formaldehyde would react with chlorine in drinking water and even with chloride ions in a worker's perspiration. He concluded that these occurrences would cause considerable problems for the entire formaldehyde industry, as well as for the melamine, phenol, and urea resin industry.

No literature sources that would substantiate Standish's claims have, however, been found.

In 1977, Marceleno wrote, in a comment to a research project (172), that preliminary disclosures had shown the presence of BCME in textile manufacturing and that there was a possibility for its formation in

chipboard manufacturing, paper manufacturing, insect-rearing laboratories, and various medical environments, including anatomy and pathology laboratories, as well as in various industrial operations in which formaldehyde and ionic chlorine compounds are utilized. Preliminary sampling results for BCME had, however, shown a lack of repetitiveness and consistency.

Earlier, in 1974, Marceleno & Bierbaum singled out four histological techniques which met the criteria for possible BCME formation, namely, the hematoxylin and eosin stain, the colloidal iron-periodic acid, Schiff-Bismarck brown technique, the Fuelgen reaction, and the Snook's reticulum stain. But when the environment in which these reactions were performed was analyzed for BCME, the results were negative (the limit of detection was however not given) (173).

Goodson (111) pointed out that BCME could be formed from hexamethylene tetramine (urotropin), which is used as urinary antiseptic, when it hydrolyzes to form formaldehyde and ammonia in the stomach where the released formaldehyde could react with hydrochloric acid.

Harris (115) replied that hexamethylene tetramine had been tested on mice and rats, with no evidence of carcinogenicity.

Owing to the fact that BCME was used in the manufacture of commercial anion exchange resins as a chloromethylating agent, Tou et al (286) made a check on such resins in order to determine whether they contained free residual BCME. The authors used the hollow fiber probe mass spectrometric technique, with a detection limit of about 10 ppb, and found no BCME. They explained this finding by the rate of hydrolysis for BCME, which is 0.012 s^{-1} (corresponding to a reaction half-time of 58 s). Thus BCME could not exist for any extended period of time in the resin solution. Besides, the commercial anion exchange resin contained about 50 % water within the beads, and, for that reason, the presence of BCME in this resin was highly unlikely.

Also CMME was used in the manufacture of anion exchange resins. Thomas (278) pointed out that, even if CMME is used in the manufacture of these resins, there is no danger of CMME exposure in the use of these ion exchange materials as they cannot contain free CMME, which quickly hydrolyzes.

On the other hand, a real danger connected with BCME was found in formalin slurries containing various Friedel-Crafts salts. In the headspaces above these slurries BCME concentrations from 0.25 ppm for ferric chloride to 1.5 ppm for aluminium chloride were found (92). Thus it was argued that any acidic solution containing chloride ions and formaldehyde should be considered as a potential source of BCME (269).

Even materials for home insulation based on urea/formaldehyde foam have been regarded as potentially dangerous by Morin & Kubinski (185) and by Garry et al (97).

In the paint industry, there might also be a possibility of BCME formation if formaldehyde and chloride ions or compounds that can release them come together (221).

Even some flame retardants can release BCME. Loewengart & Van Duuren (164, 165) showed it for THPC and Pyroset TKP, which were used in great quantities on cotton sleepwear for children (especially in the United States because of the Flammable Fabric Act of 1953). Sometimes as much as 35 weight-% of these flame retardants were applied to the fabrics.

THPC is tetrakis(hydroxymethyl)phosphonium chloride $(\text{HO}\cdot\text{CH}_2)_4\text{P}^+\text{Cl}^-$ which is synthesized from hydrogen chloride, formaldehyde, and phosphine. It degrades back to these compounds, and the freed formaldehyde and hydrogen chloride can form BCME. Pyroset TKP is a mixed phosphate/acetate salt of the tetrakis(hydroxymethyl)phosphonium cation.

Both products were found to be weakly carcinogenic in mice or, at least, to be moderately active tumor promoters. The tumor yield and multiplicity were low, but many of the tumors progressed to squamous carcinomas.

Yao & Miller (337) listed 24 instances of industrial activity in which formaldehyde is (or can be) used in the presence of chloride ions, eg, disinfecting, production and use of phenolic, urea, melamine and polyacetal resins, production of cellulose and cellulosic fibers, production of dyes, many organic chemicals, mirrors, explosives, paper and fertilizers, tanning of hides, finishing of textile fabrics, improving the quality of latices, embalming, photography, chrome printing and developing, production of pesticides, insolubilization of casein, albumin and gelatine, glass fiber bonding, manufacture and use of adhesives and laminating resins,

manufacture of particle boards, and pathology procedures. These authors also made the most extensive search for BCME so far carried out in industrial environments. For this reason they analyzed the air in eight types of plants: dye auxiliaries (resin) production, dye manufacture, fertilizer production, textile finishing on woven goods, textile finishing on knitted goods, hospital procedures (production of "gel" for burn treatment), foundry products (research plant), and foundry products (full-scale plant). The results were generally less than 0.1 or 0.2 ppb of BCME. They found that the formation of BCME in the gaseous phase was dependent on the availability of both formaldehyde and chloride ions, while the amount of water vapor in air did not seem to play an important role. In the liquid phase, however, the water content was a decisive factor.

As regards the release of formaldehyde, North (213) made experiments with finishing 100 % cotton and 50 % cotton/50 % polyester fiber broadcloth using 15 different types of resin and 7 different catalysts. His findings can be summed up as follows: The amount of formaldehyde evolved varied considerably with respect to the type of finish and the specific product. The amount of formaldehyde increased if cure time, cure temperature, and resin concentration increased or if the catalyst concentration decreased. The highest levels of formaldehyde release were found with urea/formaldehyde, melamine/formaldehyde, and carbamate resins.

The same author (212) found that cotton/polyester fabrics finished with compounds containing dimethyloldihydroxyethylene urea or with a triazone resin evolved less formaldehyde than those finished with a formaldehyde/urea copolymer or with a methylated formaldehyde/melamine copolymer.

It is probable that the affinity of formaldehyde for cellulose acts as a scavenging factor for formaldehyde (and for BCME as well). It can thus be expected that the more cotton a fabric contains the more formaldehyde it will absorb, with the consequence that less formaldehyde will be released into the air or made available for a possible BCME-forming reaction.

Formaldehyde is an efficient cross-linking agent for cellulose, in which cellulose formals and methylated cellulose formals are formed. For determining the amount of formaldehyde in these formals, a modified Schiff's method was developed by

Ramanathan et al (233). This procedure allows a colorimetric determination at 590 nm and is suitable for routine analyses.

For reducing free formaldehyde levels on cellulose fabrics, formaldehyde acceptors, especially those containing imino groups, are used (226).

The release of chloride ions originates either from hydrochloric acid or from various chlorides. With no chloride ions present or released in the reaction, there can be no formation of BCME.

As regards water, it was found that its presence in acidic formaldehyde/chloride ion systems effectively reduces the amount of BCME evolving (345, 379).

Of special importance for the present project were observations recorded about the formation of BCME from its precursors, formaldehyde and chloride ions, in the work-room air. The reports thus collected can be divided into the following four classes:

1 Reports about BCME not being formed, at least in measurable concentrations (0.1 ppb and higher), when concentrations of BCME precursors were in the lower (sub 10) ppm range (35, 71, 141, 144, 194, 363, 377).

2 Reports about the possibility of BCME formation (137, 172, 221, 355, 364, 368, 378, and a private communication from PL Spencer, Safety and Health Division, American Textile Manufacturers Institute, Charlotte, NC, of 20 November 1978).

3 Reports about actual BCME formation without explicit information about the concentrations in question (54, 72, 82, 200, 225, 369, 370, 385).

4 Reports about BCME formation with information about the concentrations in question.

As regards point 4, the following information was found:

Rohm & Haas in 1972: *Parts-per-million amounts of reactants yield parts-per-billion amounts of BCME*. (Later, it was admitted that BCME formation might be more difficult than originally assumed) (55, 352).

Eisner in 1973: *BCME concentrations of less than 1 ppb to 15.5 ppb were measured in the vicinity of reactors used to condense phenol and formaldehyde* (67).

Hurwitz in 1974: *An acrylic emulsion polymer yielded as much as 1.74 ppm of BCME in close vicinity and 2.4 ppb of BCME in the stack when ammonium chloride was used as a catalyst* (125).

Frankel et al in 1974: *BCME yields were about 0.01 mol-% from formaldehyde and hydrogen chloride. With 20 ppm of formaldehyde and 20 ppm of hydrogen chloride the result was 0.5 ppb of BCME* (92).

NIOSH Burlington Report in 1974: *A large-scale sampling yielded values of 0.4 to 8.0 ppb of BCME in textile permanent press finishing operations with formaldehyde-based resins and chloride catalysts* (371).

Textile World in 1975: *NIOSH investigations data showed BCME concentrations averaging 2 ppb and ranging from 0.5 to 8.0 ppb in the Burlington operations* (see previous item) (372).

Zollinger in 1977: *Up to 16 mol-% of oligo(oxymethylene)dichlorides were found in baths containing paraformaldehyde, water, hydrochloric acid, and acetic acid. Two-thirds of this amount can be BCME* (344, 345).

Gamble in 1977: *When animal houses were first washed down with a 15 % hypochlorite solution and then gassed with formaldehyde, a concentration of 0.2 ppb of BCME was measured at a height of 1 m* (95).

Imperial Chemical Industries (ICI) Ltd in 1978: *BCME levels in the atmosphere of the ICI Organics Division workrooms did not exceed 1 ppb for hydrogen chloride and formaldehyde concentrations below 20 ppm* (private communication from JS Gardiner of 11 November 1978).

Yao & Miller in 1979: *With the formaldehyde and hydrogen chloride concentrations in air in the low parts-per-million and sub parts-per-million range in eight different types of manufacture, in the United States, the BCME concentrations found were generally less than 0.1 or 0.2 ppb* (337).

Formaldehyde Institute and Sellakumar et al in 1980: *In air containing 14.6 ppm of formaldehyde and 10.6 ppm of hydrogen chloride, 0.1 ppb of BCME was found* (87, 255).

General atmosphere. The formation of BCME in the ambient air depends, above

all, on the availability of formaldehyde and chloride ions in air.

Important sources of chloride ions are sea air and combustion processes involving chlorine-containing fuels. At the Swedish Bohus Malmön Research Station (11°37' E, 58°35' N) chloride ion contents in sea air ranging from 0.3 to 370 $\mu\text{g}/\text{m}^3$ were measured in 1959 through 1961 (private communication from Rolf Söderlund, Meteorological Institute of the Stockholm University, 27 October 1978).

Formaldehyde occurs in urban air in amounts from 5 to 100 ng/m^3 (average 20 ng/m^3), and in rural air in amounts from 0.5 to 5 ng/m^3 . The combustion of 1 t of fuel yields the following amounts of formaldehyde: coal 2 g, oil 100 g, and natural gas 200 g (198).

In towns, motor traffic is an important source of formaldehyde, which then spreads sidewise into streets with less or no traffic and into the interior of houses (157, 247, 318). The formaldehyde content inside urban houses was found to be higher than the formaldehyde concentration outside, a finding which points to a possible formaldehyde generation or release inside the houses.

An important indoor source of formaldehyde is chipboard, especially in newly built houses. Measurements in Denmark, as reported by Andersen et al (11), yielded values from 0.08 to 2.24 mg/m^3 (average 0.62 mg/m^3). If considered against the background of the hygienic standard for formaldehyde of 1.2 mg/m^3 for occupational exposure and 0.03 mg/m^3 for continuous exposure in outdoor air, these values seem to be far from acceptable. In Sweden, the limit concentration of formaldehyde inside newly built houses is 0.1 ppm (0.12 mg/m^3). For this reason, procedures for decreasing the formaldehyde gassing-off propensity of chipboard have been developed (68, 183).

The hygienic standard of 1 ppm (1.2 mg/m^3) for formaldehyde is now under discussion and will probably be reduced in the future. Loomis (167) reported no detrimental effects at 0.5 ppm or below, while Nagornyj (192) pleaded for a reduction of the formaldehyde standard in the Soviet Union from the present 0.5 mg/m^3 (0.38 ppm) to a lower value. He also studied the effects of formaldehyde inhalation in combination with other chemicals (191).

So far, no measurements of BCME concentrations in the general atmosphere have

been made, not even in the highly polluted air of urban and industrial regions. In 1977 Sawicki (250) reviewed the potential "genotoxic" effect of BCME as formed from formaldehyde and chloride ions and concluded that – on the basis of results so far published – this BCME-forming reaction had not yet been shown to be of importance from the point of view of environmental hygiene.

An interesting suggestion was made by Hoffmann & Wynder (119), namely, that BCME might constitute a carcinogen in the gas phase of tobacco smoke, where it can be formed from formaldehyde and chloride ions, which are always present in this smoke.

Laboratory simulation experiments

After the danger of BCME as an industrial carcinogen had been recognized and after it had been found that this compound can be formed from precursors that often occur in the air at the same time, laboratory simulation experiments began to be performed in order to determine the quantity of BCME formed from certain concentrations of formaldehyde and chloride ions.

Most of these experiments were carried out from 1973 to about 1977.

Kallos & Solomon (144) studied the vapor phase reaction of formaldehyde and hydrogen chloride in air, in 1973. At relatively high concentrations of these reactants (500 to 3,000 ppm) BCME was produced in low parts-per-billion yields. No detectable BCME amounts were found when formaldehyde and hydrogen chloride coexisted in air concentrations of a few parts per million. The amount of BCME formed was less than 0.5 ppb with the following ratios of formaldehyde to hydrogen chloride in parts per million, at a relative humidity of 40 % [the reaction time (RT), in hours, is in parentheses]: 30:100 (RT 5), 30:100 (RT 15), 30:100 (RT 18), 8:100 (RT 16.5), 110:100 (RT 15), and 110:100 (RT 40). The results did not follow a definite pattern.

In 1974 Frankel et al (92) investigated the formation of BCME from formaldehyde (HCHO) and hydrogen chloride (HCl) by combining measured amounts of the reactants in glass vessels or saran bags. Atmospheres at 40 % relative humidity and 26°C were used and the results were as follows, after reaction times of 12 to 24 h (HCHO+HCl=BCME, in parts per million):

Table 2. Comparison of data concerning the spontaneous generation of bis-(chloromethyl)ether (BCME) from formaldehyde (HCHO) and hydrogen chloride (HCl).

A. Kallos & Solomon (144)			B. Frankel et al (92)			Ratio A : B
BCME (ppm)	HCHO (ppm)	HCl (ppm)	BCME (ppm)	HCHO (ppm)	HCl (ppm)	
< 0.0001	100	100	0.003	100	100	> 1:30
< 0.0005	500	500	0.023	300	300	> 1:46
0.048	3,000	10,000	0.730	1,000	10,000	1:15

4,000+40,000=5.0, 1,000+10,000=0.73,
1,000+1,000=0.13, 300+300=0.023,
100+100=0.003, and 20+20=0.0005.

Gaseous formaldehyde and hydrogen chloride reacted together in moist ambient air to form BCME in yields of about 0.01 mol-%. The amount of BCME formed was relatively insensitive to moderate changes of temperature or relative humidity but strongly dependent on reactant concentrations. Steady state conditions did not seem to be attained in less than 18 h.

Eisner (67) studied the results of the two research projects just presented and made a comparison of the formaldehyde/hydrogen chloride systems investigated by both teams (see table 2). His comments were that the two sets of results concerning the spontaneous generation of BCME were partly corroborating and partly conflicting. The corroborating data included the gas-phase formation of detectable quantities of BCME from relatively large amounts of precursors, as well as the relative stability of BCME to gas-phase hydrolysis and its relative instability to liquid-phase hydrolysis. On the other hand, the conflicting data primarily concerned the extent of BCME generation in detectable quantities from small amounts of formaldehyde and hydrogen chloride.

As regards the discrepancies in the results of Kallos & Solomon (144), on one hand, and Frankel et al (92), on the other, Eisner remarks that it is unlikely that *in situ* hydrolysis of BCME in humid air could be the cause since BCME is known to have a half-life greater than 25 h in humid air. He saw the more likely sources of these differences in the difficulties associated with accurately measuring part-per-billion concentrations of BCME and with preparing accurate concentrations of monomeric formaldehyde.

Tou & Kallos (282) studied the BCME formation in solutions in 1974. Five pairs of hydrochloric acid and formaldehyde solutions were prepared in concentrations of 2, 20, 200, 500, and 2,000 ppm. Reactions were carried out through the mixing together of 250 ml of a solution of hydrochloric acid with 250 ml of a solution of formaldehyde in a variety of combinations. These aqueous reaction mixtures were then analyzed by means of mass spectrometry employing the hollow fiber probe technique developed by Westover et al (332). No BCME was found after 18 h of stirring at room temperature, neither in the solutions nor in the headspace air. The detection limit was 1 ppb. As regards the hydrolysis of BCME, it was found that it was a pseudounimolecular reaction, that the rate of hydrolysis was independent of the concentrations of formaldehyde and hydrochloric acid, and that the pseudo first order rate constant K was 0.05 s^{-1} corresponding to a reaction half-time of 14 s.

In Britain, Davies (55) made observations in 1974 as well. His results can be summed up as follows: BCME is formed by the reaction of formaldehyde, paraformaldehyde, or hexamethylene tetramine with acid chlorides such as hydrogen chloride, chlorosulfonic acid, phosphorus trichloride, and aluminum chloride. It can be readily hydrolyzed by water and alkalis back to formaldehyde and hydrogen chloride.

Work in the ICI laboratories gave general support to the Rohm & Haas findings but indicated that, in some instances, BCME formation is more difficult than the initial Rohm & Haas report suggested.

At ICI, no BCME formation was detected in concentrations of more than 1 ppb when the reactants were present at levels several times their hygienic standards (2 ppm for formaldehyde and 5 ppm for hydrogen

Table 3. Surface effect of bis(chloromethyl)ether on various materials.

Reactor material	Temperature (°C)	Concentration of water vapor (vol-%)	Relative humidity (%)	Rate of hydrolysis (min ⁻¹)	Reaction half-time (h)
Glass	25	2.2	67	0.00057	20
Fused ground glass	25	2.6	81	0.00047	25
Saran coated with ferric oxide	23	1.2	42	0.0013	9
Saran coated with ferric oxide	23	2.3	81	0.0016	7.2

chloride) and when the relative humidity was over 50 %.

As regards aqueous media, BCME formation is considerably more difficult than initially proposed. Free BCME introduced into such media disappears rapidly. In nonaqueous media part-per-million levels of reactants are expected to yield part-per-billion levels of BCME. Practically no prediction regarding the resultant BCME concentration is possible even if reactant concentrations and reaction conditions are known. Only experiments can decide the issue. If chlorides are present, the BCME formation is enhanced.

Tou & Kallos (283) investigated the stabilities of CMME and BCME in 1974, and their conclusions were as follows: In humid air the rates of hydrolysis are 0.31 to 0.0018 min⁻¹ for CMME and 0.0016 to 0.00047 min⁻¹ for BCME depending upon the reactor wall surface, as there is a strong surface effect that influences the rate of hydrolysis. The following decreasing order as regards the intensity of the surface effect was observed: saran coated with ferric oxide > glass > Teflon® > saran.

The effect of the surface on the rate of hydrolysis must be considered when chemical equipment for BCME and CMME investigations is designed. BCME is relatively stable in air, and its monitoring should not present any difficulties. Table 3 shows the surface effect of various materials on BCME.

In Holland calculations were made in 1975 at the MCN Methanol Chemie Nederland vof, Delfzijl, as to whether the formaldehyde and hydrogen chloride emissions in two works could lead to the formation of dangerous BCME concentrations in air (61). With the use of Frankel et al's data (92) and the standard formula for the equilibrium constant *K* (with water vapor in air being considered) the results were $K=5 \times 10^4$ to 2.7×10^8 .

When $K=10^8$ (mol/l)² and concentrations of 2 ppm for formaldehyde and 5 ppm for

hydrogen chloride were used, the calculated value for the BCME concentration in air was 10⁻⁶ ppb. Thus it was concluded that there was no danger of BCME forming on the premises or in the vicinity of the chemical plants in question.

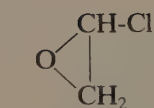
Other calculations included the rate constant of BCME formation, which was found to be 23.5 min⁻¹ (mol/l)² and which corresponds to a reaction half-time of several seconds only.

Tou & Kallos (284) studied the formation of BCME in reactions of formaldehyde with chloride ions in 1976 using both hydrogen chloride and various chlorides (sodium chloride, calcium chloride, magnesium chloride, and ferric chloride). The reaction systems were too diluted with water, and therefore no BCME was found in the headspace air at the detection limit of a low part-per-trillion range. The reactions were run at room temperature, and a carrier gas was blown through the reaction system.

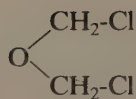
In 1976 Alvarez & Rosen (7) investigated the formation and decomposition of BCME in aqueous media using chloromethylating mixtures of the hydrogen chloride/formaldehyde/zinc chloride type. It was shown that BCME was formed rapidly at low levels (100 ppm) and attained fairly steady concentrations of 300 to 500 ppm in the headspace air. The standard chloromethylating mixture contained 1 g of paraformaldehyde, 6.2 g of 37 % hydrochloric acid, and 8 mg of zinc chloride.

Analogous substances

A near BCME analogue is chloroethylene oxide, which is the effective metabolite of vinyl chloride monomer. There is a structural similarity between BCME and chloroethylene oxide (21, 22, 339):



chloroethylene
oxide



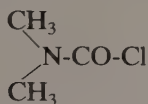
bis(chloromethyl)-
ether BCME

Most work on BCME analogues and chemically similar substances from the point of view of mutagenicity and carcinogenicity was done by Van Duuren and his group at the New York University Medical Center.

In 1972 Van Duuren et al (308) tested six chloro compounds related to BCME for their carcinogenic activity. The rates of hydrolysis were correlated to chemical reactivity and carcinogenicity. The carcinogenicity of the compounds was related to their alkylating activity and molecular flexibility. It was argued that reactions with nucleic acids were not necessarily the critical steps in carcinogenesis.

In 1974 a team led by Van Duuren investigated 17 direct-alkylating chloroethers and other compounds and discovered the high carcinogenic potential of dimethyl carbamoyl chloride (DMCC) (305). This compound was found to have – like BCME – a rapid rate of hydrolysis with a reaction half-time of minutes, at a physiological pH value and temperature. Carcinogenic sulfates, sultones, epoxides, and lactones had much longer reaction half-times in hydrolysis.

Dimethyl carbamoyl chloride having the formula



is synthesized from trimethyl amine and

phosgene and is used as a reagent in the manufacture of dyestuffs, pharmaceuticals, and herbicides. By 1975 more than 50 patents relating to its uses had been issued (86, 201, 304, 375, 376).

Several chlorinated alkanes were also investigated (such as chloromethanes and chloroethanes in various degrees of chlorination) (380, 382).

Further work on chloroethers was done in 1975 and 1976. Van Duuren et al (307) investigated bifunctional and trifunctional alpha-chloroethers and found that some of them were carcinogenic. Nelson (200) investigated 11 halogenated compounds and found that bifunctional alpha-haloethers were more active than their monofunctional analogues. With increasing chain length and with the chlorine atom moving away from the ether oxygen atom, carcinogenic activity decreased. The more carcinogenically active compounds were the most labile, and the mutagenic activity roughly paralleled the carcinogenic activity.

In 1980 Weisburger & Van Duuren (322) commented on a publication (113) concerning dichloromethyl methyl ether ($\text{CH}_3\text{OCHCl}_2$), which has the same general formula as BCME ($\text{C}_2\text{H}_4\text{OCl}_2$) but – in contrast to BCME – has an asymmetric structure. This compound, which is a very useful intermediate in many organic syntheses, was presented as noncarcinogenic, and reference was made to one of Van Duuren et al's earlier publications. Weisburger & Van Duuren pointed out that, after all, this compound could be a nasal cavity or lung carcinogen and that, besides, it is prepared in a dangerous way, namely, via CMME, with the attendant risk of BCME formation.

Mutagenicity and carcinogenicity of bis-(chloromethyl)ether and its precursors

BCME and (to a less extent) CMME are mutagenic and carcinogenic substances, and so is also at least one of the precursors of BCME, namely, formaldehyde, both alone and in combination with chloride ions, according to the latest research results.

Formaldehyde

The mutagenicity and carcinogenicity of formaldehyde deserve due attention in BCME research, as there might be some connection between the effects of formaldehyde and those of BCME.

Formaldehyde was found to be mutagenic in *Drosophila melanogaster* (14, 15, 16, 17, 145, 216, 235, 236), in yeast (53), in *Pseudomonas fluorescens* and *Escherichia coli* (74, 208, 335), in the tickborne encephalitis (TBE) virus (340), and in the *Chaetomium aureum* chivers (105).

It was shown that the point of attack of formaldehyde on deoxyribonucleic acid (DNA) was the adenine moieties of DNA (3, 4, 147).

As regards the mechanism of nucleic acid modification, it was found that formaldehyde can fix opposite structural states, the native and the denatured. The denaturation of the nucleic acids is fixed by the formation of methylol derivatives, while the native macrostructure of the polymer is fixed by methylene cross-links formed in a secondary reaction (77). Thus adenine dimers are formed by means of methylene bridges (227).

It was also suggested that the mutagenic action of formaldehyde was associated with the action of the reaction products of formaldehyde and amino-containing compounds on DNA (256, 262). Previously it was thought that the mutagenic mechanism of formaldehyde involved a formation of peroxides that led to free radicals (60).

Other publications on the mutagenicity of formaldehyde include the early work of Fraenkel-Conrat and his team, who concentrated on proteins (as supposed heredity carriers, in 1948) (89, 90), and research on the ability of inducing unscheduled DNA synthesis in HeLa cells (175), on the irreversibility of cross-linked DNA (261), and on the effect of hydrolyzed formaldehyde-treated ribonucleic acid (RNA) on neoplastic and normal human cells (78). More general treatments of the mutagenicity problem were written by Fishbein (80, 84), and a monograph on genetic and cytogenetic effects of formaldehyde and related compounds was written by Auerbach et al (18).

The embryotropic effects of formaldehyde were studied by Gofmekler and his co-workers (107, 108).

A report about atypical proliferation of the bronchial epithelium under the influence of formaldehyde was published as early as 1935 (98), but, as regards the carcinogenicity of formaldehyde, the first hints were given in 1954–1955 when Watanabe et al (319, 320) reported having provoked sarcomas in mice by means of subcutaneous injections of formaldehyde and hexamethylene tetramine

solutions. In 1951, Boyland & Sargent (41) provoked a local greying of hair in mice by means of an intradermal application of formaldehyde. This phenomenon is known to occur with chemicals that are mutagenic or carcinogenic or both (a radiomimetic effect). Formaldehyde was earmarked as a potential carcinogen by Horton et al in 1963 (121) and by Rosenkranz in 1972 (243).

Real evidence for the inhalation carcinogenicity of formaldehyde was first reported in October 1979. Preliminary data from an ongoing inhalation study of rats and mice, sponsored by the Chemical Industry Institute of Toxicology (CIIT), indicated that for exposures of 15 ppm for 6 h/d, 5 d/week for 18 months, formaldehyde was carcinogenic in rats. Several of the animals developed cancer by the 12th month. The cancer type was squamous-cell carcinomas originating in the epithelium of the nasal turbinates. According to the interim report at the 3rd CIIT Conference on Toxicology (November 1980), a total of 93 rats from the stock of 240 animals in the 15-ppm exposure group developed squamous-cell carcinomas of the nasal turbinates, whereas two rats developed respiratory epithelial carcinomas. Furthermore, two rats exposed to 6 ppm and two mice exposed to 15 ppm of formaldehyde also developed squamous-cell carcinomas of the nasal turbinates (48, 88, 197, 257, 386, 387).

The formaldehyde concentration that provoked most carcinomas (15 ppm) is about one-thirtieth of the LC₅₀ value for both rodent species (193).

Swedberg et al (271) remarked in this connection that, in contrast to humans, rats and mice are obligatory nose breathers. Thus the site and degree of formaldehyde toxicity may be modified in humans. As an example, they cite BCME, which induces nasal tumors in rats but lung tumors in humans.

So far, no adequate epidemiologic studies seem to have been carried out which would address the problem of formaldehyde carcinogenicity in humans. On the other hand, many people have been exposed to formaldehyde over the last 100 a or so without trouble other than that arising from primary irritation and sensitizing (388).

In former years, the formaldehyde concentrations to which workers were exposed might have been anything up to 20 ppm, which is considered the maximum human tolerance level at present (97).

Formaldehyde and chloride ions

A simultaneous breathing of formaldehyde and chloride ions in concentrations of less than the hygienic standard in air was found to reduce the mitochondrial respiration of exposed rats, but no cancers were found (23). The first report of a mixture of formaldehyde and chloride ions in air causing cancer in rats came from Nelson in 1979 (385). A group of 100 male rats were exposed to 14.6 ppm of formaldehyde and 10.6 ppm of hydrogen chloride in air. There were, on the whole, 544 d of exposure, 6 h/d over a period of 814 d in this experiment. Twenty-five rats developed squamous-cell carcinomas of the nasal cavity, and two developed papillomas of the nasal cavity (87, 197, 255).

So far, it is not known whether the nasal cancers observed in this mixed exposure study were caused by formaldehyde, hydrogen chloride, BCME (of which there was 0.1 ppb in the formaldehyde/hydrogen chloride mixture in air), or some combination of these substances.

Bis(chloromethyl)ether

Carcinogenicity and mutagenicity in animals and cell systems

The haloethers BCME and CMME are both mutagenic and carcinogenic. Their carcinogenicity was discovered earlier than their mutagenicity.

Using the Ames test with *Salmonella typhimurium* and *Escherichia coli*, several researchers discovered the mutagenicity of BCME and CMME, as well as that of some chemically related compounds (9, 10, 178, 179, 190).

The discovery of the carcinogenicity of BCME did not follow the usual pattern, ie, epidemiology followed by bioassay followed by chemistry. The order was reversed, the first consideration being the chemical structure and reactivity in the case of alpha-chloroethers (302).

The present assessment of BCME is that this substance is a direct-acting inhalation carcinogen of radiomimetic character [like, eg, sulfur mustard, bis(2-chloroethyl)sulfide].

The work leading to the discovery of BCME carcinogenicity was facilitated by re-

search in which it was attempted to induce lung cancer in animals. First of all thread transfusion and pellet implantation techniques were tried (151), but real progress was achieved only after Laskin had developed elaborate exposure chambers which permitted controlled exposures of animals to respirable dusts and gases (202).

In reviewing the work done by the Van Duuren group, Nelson et al characterized the consequences of the direct-acting carcinogenicity of BCME as follows (203):

It is in the nature of direct-acting alkylating agents that they have a high likelihood of altering intracellular DNA and producing mutations. Such interactions may constitute the initiating step in the induction of cancer. Whether cancer actually results from tissue contact with such agents is determined by many different factors, some quantitative in nature, some qualitative. As a minimum, access to the critical biochemical unit (DNA) is required in the appropriate dosage [p 5].

In studies of the reactions of BCME with DNA it was found that BCME interacted with the guanine and adenine moieties of DNA (94, 109). The extent of BCME incorporation by DNA was found to be 13 times higher than that of formaldehyde. Slaga et al (263) found that BCME first inhibited and then stimulated the synthesis of DNA, while CMME remained inactive.

Shooter (260) experimented with the effect of various alkylating agents on the bacteriophage B 17 and came to the following conclusion as regards BCME:

Indeed, the results provide no evidence for any direct action of the ether on the nucleic acid of the bacteriophage, the inactivation observed being roughly equal to that produced by the formaldehyde generated The present results suggest the possibility that the chloromethyl ether may be transported to the nuclei of cells and when hydrolysed close to the genetic material the formaldehyde produced may be the proximal carcinogen [p 583].

A similar effect of formaldehyde transfer from a formaldehyde-releasing compound to the DNA was observed by Probst et al (230). In this particular case the formaldehyde vector was the N-Mannich base N-(isonicotine amidomethyl)sarcosine. The authors stressed that this compound protects the active formaldehyde from reacting with components of the outer cytoplasm on its way towards the DNA of the cell.

In 1968 and 1969, CMME and BCME were tested on mice by Van Duuren et al

using skin application, subcutaneous and intraperitoneal injections (301, 303). BCME was found to be a potent alkylating carcinogen, whereas CMME was inactive. Twelve years later, in 1980, Zajdela et al (339) used the same technique in order to compare chloroethylene oxide (as the effective metabolite of the vinyl chloride monomer) and BCME.

In 1969, Gargus et al (96) reported having produced adenomas by subcutaneously injecting BCME and CMME into newborn mice. The induction period was only six months. As to the criticism that might be leveled against the use of reputedly highly sensitive newborn animals, Toth, who reviewed experiments with carcinogenic chemicals, came to the conclusion, that, on the contrary, more tumors are sometimes produced in older animals (281).

In 1971, Laskin et al (154) found that an inhalation of 0.1 ppm of BCME was highly carcinogenic in rats, and a general warning was issued in view of the potential hazard to individuals occupationally exposed to this alkylating agent.

Of special importance was the three-part study published in 1975. In the first part, Drew et al (66) investigated the acute inhalation toxicity of CMME and BCME. The respective data have been presented in the section on the properties of BCME. In the second part, Laskin et al (153) exposed rats and hamsters to 1 ppm of CMME 6 h/d, 5 d/week, throughout their lifetimes. CMME was found to be a much weaker carcinogen than BCME, and it was even conjectured that the active agent in this case was not CMME but BCME, which the technical grade CMME contained in amounts of about 1 to 7 %. In the third part, Kuschner et al (152) reported on rats and hamsters that had been exposed to 0.1 ppm of BCME in air, 6 h/d, 5 d/week, throughout their lifetimes. Additional groups of rats were given 10 to 100 exposures at 0.1 ppm of BCME in air and then held until they died. Forty cancers of the respiratory tract were found in 200 animals (14 cancers of the lungs and 26 cancers of the nasal cavities). The percentage incidence of cancer was directly related to the number of exposures in the following way: 10 exposures 2.4 %, 20 exposures 6.5 %, 40 exposures 22.2 %, 60 exposures 22.2 %, 80 exposures 44.1 %, and 100 exposures 60.0 %.

Besides the aforementioned university research there was also research work done by

the US chemical industry.

A research project reported in 1973 concluded that BCME was probably a carcinogen but that the evidence about CMME was inconclusive (161).

In 1975, Leong et al (159) reported experiments performed in Dow's Toxicology Research Laboratory, where groups of rats were exposed to 100, 10, and 1 ppb of BCME in air, for 6 h/d, 5 d/week, for six months. Es-thesioneuroepitheliomas were found in the 100-ppb exposure group, but no neoplasms were observed in the 10- and 1-ppb exposure groups.

The results of animal experiments with BCME and CMME were summed up by Lawley in 1976 (156) and by Tomatis et al in 1978 (279). As regards the carcinogenicity of CMME, Taylor & Simon reported in 1974 that this substance – when purified (ie, not containing BCME as a contaminant) – also exhibited some carcinogenic potential of its own (274).

Bettendorf (31) summed up the tumorigenous effects of BCME on animals as follows:

- a. skin painting in mice: papillomas and carcinomas;
- b. subcutaneous injections: local benign and malign mesenchymal tumors (fibromas, fibrosarcomas, lymphoblastomas);
- c. Subcutaneous injections in newborn mice: lung adenomas;
- d. inhalation in rats and mice: es-thesioneuroblastomas in the nasal cavity, as well as adenomas and carcinomas in the airways.

Carcinogenicity in humans

The majority of BCME-caused deaths were found in the United States, the Federal Republic of Germany, and Japan.

Most of the BCME carcinogenicity research has thus far been carried out in the United States, especially by two research teams, the New York University Medical Center group with Van Duuren, Nelson, Drew, Laskin, Kuschner, etc, and the Philadelphia group with Weiss, Figueroa, Boucot, etc.

The first group began by being interested in the chemical tracking of carcinogens, they then switched to animal experimentation and finished with epidemiologic investigations. The second group was primarily interested in the effects of BCME and CMME

on the human lungs and in epidemiologic investigations.

Evidence of lung carcinogenicity. In 1972 it became known that four workers employed in the chemical plant of the Diamond Shamrock Co in Redwood City, CA, died because of exposure to BCME. At that time, two other workers who had also contracted lung cancer were still alive. According to the death certificates, the four dead workers (who died in 1964, 1965, 1968, and 1971) suffered from lung cancer. Their ages ranged from 32 to 48 a, which is considered to be under the age when smoking could be considered a cause of fatal lung cancer. The smoking histories of these workers were, however, not clear (349).

The suspicion that BCME might be the causative factor in lung cancer arose actually as early as 1965 after the first two of the aforementioned cancer deaths of workers who handled CMME in the manufacture of ion-exchange resins. When later other deaths followed, it was believed that a risk was present in exposures which were longer than 5 a.

In 1973, the *Lancet* gave further particulars about the conditions under which the BCME-caused deaths occurred (359).

In a chemical factory employing 200 workers, an excess of lung cancer was suspected as early as 1962, and regular radiographic examinations of the lungs were carried out twice a year. Over the next 5 a, a group of 125 men were studied. Of the 111 workers who could be traced, four (aged 35 to 54 a) developed lung cancer (a 5-a incidence of 5.54 % against the 0.57 % predicted). In the manufacturing process CMME was used, and the supervision of the mixing process was not very good, as there were frequent gross evolutions of fumes at short intervals during the shift. The report states that the employees considered it a good day if the entire building had to be evacuated 3–4 times during the shift because of obnoxious fumes. Of the 14 men aged 35 to 55 and for whom a diagnosis of lung cancer was made in 1961–1971, all but two had oat-cell cancers. Three of them were nonsmokers.

The management was not however sure that the causative factor was CMME or – more precisely – the BCME contained as an impurity in CMME.

In the meantime research was made as regards the chemistry of haloethers. In 1969

Van Duuren et al (311) investigated five haloethers, and the biological activity of CMME and BCME was found to be surprising in view of their rapid rate of hydrolysis. It was inferred that critical interactions involved in carcinogenesis must occur very rapidly with compounds of this nature.

In 1972, Van Duuren et al (310) called attention to the fact that BCME and CMME were direct-acting carcinogens that required no metabolism in vivo to produce proximal carcinogens. This finding explained their acting at the site of exposure (lungs for airborne BCME).

In 1973 it was established beyond doubt that BCME was the causative factor in haloether carcinogenesis. This fact was communicated to the chemical manufacturers concerned. The consequence was that the Institute of Environmental Medicine of the New York University was requested to undertake a systematic industrywide study on BCME in seven chemical companies (199).

As early as 1975, Albert et al (1) reviewed the results of the study involving 1,800 workers who had been exposed to CMME from 1948 to 1972 and about 8,000 workers who served as referents. The risks for various exposure groups were calculated, and it was found that CMME had a clear life-shortening effect. Those who died of respiratory cancer due to CMME lost an average of 25 a of life.

By 1977, according to Bettendorf (31, 32), 60 cases of BCME-caused lung cancer became known in the most industrialized countries of the world. The average age at diagnosis was only 45 a, and the average exposure was 7.4 a.

One of the latest cases that became known concerned a 42-year-old German research chemist who died of an extensive lung carcinoma after having experimented for 7 a with BCME, CMME, and, on a smaller scale, dimethyl sulfate (33). Reznik et al (239) reported the case of a chemist who started to experiment with BCME and CMME at the age of 30 and in whom a lung cancer was diagnosed 12 a later. It is not clear whether Bettendorf (33) and Reznik mean the same person.

Lung cancer deaths due to BCME were observed at BASF, Ludwigshafen a.R., in the Federal Republic of Germany.

Besides an accident in which a young student-worker spilled some BCME on himself and later died as a consequence of the re-

spective injuries sustained, there were, according to Thiess et al (277), eight cases of lung cancer in men who had worked in the production and application of BCME. Their average age at diagnosis or death was 52.5(SD 11.1) a, the average exposure time was 6.6(SD 1.2) a, and the average latency period from first exposure to diagnosis was 12.3(SD 3.8) a.

In 1981 Norporth (209) reported that the number of BCME-caused lung cancer deaths in the Federal Republic of Germany was 20 cases, of which 12 were due to direct exposure to BCME and 8 occurred in workers employed in chloromethylating reactions. The 12 direct exposure cases contained the eight cases reported by Thiess et al. Norporth mentioned that the BCME risk in the chemical industry was greater than usually supposed because BCME can be formed in many chemical processes, eg, in phosgene chemistry, in isocyanate chemistry, etc.

It is supposed that, in spite of an apparent lack of original German publication, the German chemical industry has been devoting much effort to the problem of chloroethers and that there is a relatively large mass of results and experiences available for strictly internal use.

This assumption might apply also to the chemical industry of other countries. For example, as far as Switzerland is concerned, the only communication found in the Swiss medical press was a note by Schlegel (252) commenting on an article by Figueroa et al of 1973 (79).

On the other hand, the Swiss chemists' contribution to the problems of haloether analysis has been considerable (50, 69, 70, 71, 72, 112, 345). A plausible interpretation is that the BCME problem proved to be of great practical importance in the Swiss chemical and pharmaceutical industries. Alkylating reactions are important modification processes in the pharmaceutical industry, eg, in the manufacture of alkaloid derivatives.

In Japan, Sakabe (246) investigated the lung cancer deaths in a dyestuff factory where five workers who had been exposed to BCME died of lung cancer. The risk was calculated to be 208 times higher than expected in the general population.

The Japanese experience is valuable because the population in which the BCME-induced cancers were observed was very small and closed, and it was possible to determine exactly who had been exposed to BCME.

The cancer occurrence in this study was 12 %, while, eg, American investigations came to figures of 3 to 5 % only.

In the American and German studies it was difficult to determine which workers of the groups under study had actually been exposed to BCME or CMME. For this reason, larger groups were taken into consideration, and the number of the exposed persons was probably exaggerated. If the real number of BCME-exposed persons had been used as the basis for calculation, it is probable that the percentage of lung cancer death would have been higher (158).

Actually the latest calculations concerning the BCME-exposed workers at the Rohm & Haas Co show an observed to expected ratio of 77 (110). A former assessment made in 1976 by DeFonso & Kelton (56) revealed a relative risk of lung cancer which was 3.8 times higher in the 669 exposed versus the 1,616 nonexposed workers. There were, on the whole, 20 cases of lung cancer, with five more which were uncertain.

In the United Kingdom, where CMME was produced on a regular basis in two factories for several decades, it was revealed, in 1973, that there was no excess of overall cancer deaths from lung cancer among the workers in these factories (359). Considered against the background of experiences made in the United States and in the Federal Republic of Germany, this result is liable to raise some doubts. It is probable that more will be known in the future. In 1977 the British Office of Population Censuses and Surveys in London announced that they were working on a survey of workers exposed to BCME (333). So far, no results have been published.

In France, no active BCME research has been done, judging by the character of the literature (168, 184). Even Méry's medical doctorate thesis of 1975 (180) relied entirely on foreign material.

Type of induced cancer. In humans, only lung cancer has been attributed to the effect of BCME, although even other types of cancer have been observed in animals (see the section on the carcinogenicity and mutagenicity in animals and cell systems).

In 1977 Pasternack et al (225) reviewed the results of the industrywide epidemiologic study made to evaluate the human carcinogenicity of BCME and CMME. The following findings are of particular importance:

It should be noted that the predominant histologic type of bronchogenic cancer reported in CME-exposed workers has been small cell-undifferentiated or oat cell carcinomas. A similar predominance of this histologic type has been noted for bronchogenic cancers associated with radon daughters and with nitrogen mustard. By way of contrast, the predominant type associated with cigarette smoking is squamous cell carcinoma.

It is also noteworthy that most, but not all, of the men who developed lung cancer had smoked cigarettes. The fact that some nonsmokers are in the group and that the lung cancers occur at much younger ages and are of a different cell type than normally found with cigarette-induced lung cancers provide further evidence that BCME is a primary agent, rather than cigarette smoke [p 745].

Wegman & Peters (321) commented on the relative occurrence of oat-cell or small-cell carcinomas. In the general population of the United States about 20 % of all lung tumors are classified as such carcinomas. In populations occupationally exposed to asbestos, arsenic, chromium, and uranium, the proportion of this type of lung cancer is 38 to 64 %. Even higher is the proportion of this cancer type in BCME-exposed persons. In the Los Angeles transport workers investigated from 1968 to 1970, it was found that, by cell type, the proportion of oat-cell cancer was twice as high as in the total white male population.

Internal combustion engines (of both Otto and Diesel type) have formaldehyde in the exhaust gases, and the air blown over the region from the sea contains an increased amount of chloride ions. Thus there might be a possibility of either direct BCME formation in the air or of a simultaneous effect of formaldehyde and chloride ions.

Unfortunately, the preferred oat-cell type of cancer in the haloether-exposed persons is not likely to be of much help in epidemiologic studies because urban and industrial environments also contain other carcinogens that can cause the same type of cancer. This situation is in contrast, eg, to that of asbestos or vinyl chloride monomer, both of which cause very specific and rare types of neoplasms (mesotheliomas for the former and liver angiosarcomas for the latter) (40).

The 1979 summing-up of the International Agency for Research on Cancer (IARC) (6), which completed and corrected the previous reports of 1973 (128, 129), mentioned the fact that the studies had shown a positive association between atypical cells in bronchial excretions (abnormal pulmonary cytology)

and exposure to BCME which was not related to cigarette smoking.

Dose-response relationships. According to the IARC report of 1979, several studies have found a significant excess of lung cancer among BCME- or CMME-exposed workers; this excess was directly related to intensity and duration of exposure, the excess respiratory cancer mortality being the most marked in workers under 55 a of age (6).

The exposure categories were however only approximate, as no concentration measurements were made at the time when the cancers were contracted.

It is however possible to use a simple logical treatment which is based on several ascertained facts and which produces plausible results (288, 290).

What has become known in the course of the CMME and BCME research and can be used as a basis for calculations are the following facts: (i) the present hygienic standard for BCME is 1 ppb in air, (ii) the concentration of 0.1 ppm (100 ppb) of BCME in air has been found to be potentially carcinogenic in animals, (iii) the chloroether exposures in the chemical industry concerned mainly CMME, (iv) the technical grade CMME which was used as a reactant contained 1 to 8 % of BCME, (v) the workers in whom later lung carcinomas developed might have been (at least intermittently) exposed to 1 to 10 ppm of technical grade CMME in air, (vi) the concentration spread of BCME in the workroom air, as determined by actual analyses of ambient air in industrial operations that involved the simultaneous use of formaldehyde and chloride ions, was from 0.1 to 10 ppb, and (vii) a concentration of 0.1 ppm of BCME was measured in an atmosphere that contained 14.6 ppm of formaldehyde and 10.6 ppm of hydrogen chloride and that proved to be carcinogenic in animals.

On the basis of the preceding premises the following conclusions can be drawn:

- a. the workers that contracted lung cancer might have been exposed to BCME concentrations in air ranging from 10 to 800 ppb;
- b. the average time-weighted exposure might have been somewhere between 10 and 100 ppb of BCME in air;
- c. most cancer cases, especially those with conspicuously short latency periods, might have been caused by exposures superior to 50 ppb of BCME in air;

d. if at least a part of the animal carcinomas in point vii were due to BCME, then the (relatively) safe concentration of BCME in air would have to recede into the part-per-trillion range, a situation similar to that which has been suggested for benz(a)pyrene (258).

Point d presents a strong argument for the surveillance and monitoring of those workplaces in which formaldehyde and chloride ions occur at the same time (155).

The question is, of course, whether there can be a safe threshold for BCME.

Maugh (176, 177) reviewed the scientific bases for the regulation of chemical carcinogens and paid special attention to how dangerous small doses can be. He pointed out that the more conservative view about there being no thresholds had been in ascendancy in the last few years. With BCME, which is considered the most potent carcinogen so far discovered (217) and which is a radiomimetic substance, it is prudent to assume that there is no threshold.

As regards the comparative mortalities from BCME on one hand and from vinyl chloride monomer (with chloroethylene oxide as the proximal carcinogenic metabolite) on the other, it is of interest to point out the following findings: As of 1977 there were 64 cases of recognized liver angiosarcoma due to vinyl chloride monomer, with an average latency period of 21 a, and as of 1975 there were 61 cases of recognized bronchial carcinoma due to BCME, with an average latency period of 12 a (66 % of the oat-cell type).

The average carcinogenic concentration of vinyl chloride monomer that caused the registered cancer deaths is supposed to have been between 200 and 1,000 ppm, while the average carcinogenic concentration of BCME – as shown by the aforementioned calculation – might have lain between 10 and 100 ppb (85, 180, 267, 291).

It is also of interest to determine whether a single exposure to a high air concentration of BCME can lead to the development of lung carcinoma, as was found, for example, with massive exposures of rats and mice to vinyl chloride monomer of the order of 5,000 to 50,000 ppm for 1 h (383).

As there were no recorded instances of such single massive exposures to haloethers, attempts were made to use information about mustard-gased soldiers from World War I (26, 46, 120). The results were, how-

ever, not conclusive. On the other hand Japanese investigations of former employees of a poison gas factory confirmed the high carcinogenicity of mustard gas in prolonged exposure (314).

It was found that there were similarities in the lung cancer picture of uranium miners and the lung cancer caused by radiomimetic substances, such as BCME and mustard gas (315).

Investigations concerning the occupational risks of chemists, both in the United States and Sweden (162, 220), brought no relevant information as they were not compound specific.

Interactions. The most important interaction with BCME in the causation of bronchial carcinoma is cigarette smoking. This confounding factor was studied by the Philadelphia research group headed by Weiss.

The work of the Philadelphia group was connected to the Philadelphia Pulmonary Neoplasm Research Project, which was started on 4 December 1951 and which investigated a group of male volunteers, originally 45 a old, who were followed for 10 a (39).

In 1973 Figueroa et al (79) reported on the then known 14 cases of BCME-caused lung cancer in an American chemical company. The victims were rather young, being mostly in the fourth or fifth decade of their lives. Their average age was 44.8(SD 6.6) a at diagnosis. Three of the 14 never smoked and 12 of the histologically confirmed cancers were of the oat-cell type.

In 1975 Weiss & Boucot (328) reported on a prospective study of 125 workers planned for 10 a to investigate the incidence of lung cancer. Some of the men had been exposed to BCME. They had symptoms of chronic bronchitis more often, but the lung ventilating function was not significantly affected by the chemical exposure. It was found that CMME or its contaminant BCME were more potent carcinogens than cigarette smoking. The percentage of small-cell carcinomas was very high in the cases of haloether-induced cancers in comparison to the about 20 % found among nonexposed cigarette smokers. There was an increase of dyspnea, but without concomitant changes in the radiological picture of the chest to explain it.

A year later, further particulars were reported by Weiss (323). The inverse relation of lung cancer to cigarette smoking in the

group of workers under investigation was surprising and in marked contrast to the findings in uranium and asbestos workers. This finding seemed to indicate that the chronic bronchitis induced by smoking with its bronchorrhea might be a protection against the carcinogenic character of the haloethers.

In 1976 Weiss & Figueroa (330) compared the induction periods for haloether-induced cancers with the smoking-induced cancers from the Philadelphia Pulmonary Neoplasm Research Project. With haloethers the induction period was 10–24 a and with smoking it was 35–53 a. It was concluded that the ability of the haloethers to cause cancer in nonsmokers was a striking phenomenon since other industrial carcinogens, such as asbestos and radon daughters, rarely induce cancer without smoking being an essential cofactor. The fact that haloethers produced a high majority of small-cell cancers was also considered to be a factor of biological significance.

In 1977, a report on the study of 125 male workers was published by Weiss (325). The inverse relationship between smoking habits and the risk of lung cancer was stressed again.

Weiss (324, 326) tried to find a method for revealing differences between the exposed and nonexposed workers. He investigated both the 1-s forced expiratory volume and the end expiratory flow rate.

Weiss and his co-workers pursued their investigations and in 1979 summed up the results of an epidemiologic study covering the period from 1948 to 1971 in a chemical plant where workers were exposed to CMME and BCME in varying degrees and for various exposure durations (331). It was confirmed that small-cell carcinoma was a specific response to the inhalation of haloethers.

In a publication of 1980 (327) Weiss came to the following conclusion:

The risk was higher in men who were not smoking cigarettes at the start of the observation than in those who were. This difference was even more impressive when examined in relation to the risk of lung cancer by smoking habit in the general population. The data suggest that continued cigarette smoking entailed a factor which partially inhibited the carcinogenic effect of chloromethyl ethers [p 527].

Weiss did not, however, stress that cigarette smoking is a protection against BCME risk, and in his reply to Goldsmith's objections (110) he confirms that the

cigarette smokers among the chloroether workers had a much higher risk than workers in the general population.

Thus, the haloethers are markedly different from other carcinogens in that they do not require smoking as a contributing factor for the development of lung carcinomas (as, eg, in the case of asbestos).

The research done by the Philadelphia groups was probably the first of its kind to be brought to the attention of the general public outside the United States (358).

Short history of regulation

The discovery of the carcinogenicity of BCME and CMME was a dramatic event in the history of occupational medicine, as described by Randall & Solomon (234). The regulation-seeking part of these events can be summed up as follows: Though there was an "awareness" of disease, probably lung cancer, of uncertain origin even before 1972, it seems that a communication in that year about six haloether-exposed workers having contracted lung cancer was the beginning of serious public concern (349). This discovery and later communications led to a campaign for a regulation to end occupational exposure to these compounds (350, 351, 353, 354). In 1974, an "Emergency Temporary Standard on Certain Carcinogens" was published for BCME, CMME and 12 other carcinogens (356). Later in the same year employers were required to report their medical surveillance programs and monitoring systems for carcinogens in their enterprises (357).

As early as 1973, the *Lancet* published some information about the work conditions in the American chemical factory in which the haloether cancer deaths were first observed (359). Permanent standards for the 14 carcinogens were being prepared, but the American chemical industry was against them (360). In 1974, descriptions of the 14 carcinogens with the attendant hazard reviews by NIOSH, as well as final rules for both haloethers, according to the Occupational Safety and Health Act, were issued (361, 362).

There was a controversy about whether a possible cancer occurrence in man can be inferred from a cancer occurrence in animals, and the Environmental Protection Agency (EPA) was obliged to issue a positive statement on this problem (373).

In 1976, NIOSH started work on "recommended exposure standards" which were to appear in 1979 (374). The threshold limit value (TLV) list published by the American Conference of Governmental Industrial Hygienists (ACGIH) contains a threshold limit value of 1 ppb for BCME but none for CMME (8). In 1978, the EPA was reported to be working on effluent standards for "priority pollutants," but waterborne BCME was not considered a risk because of its ease of hydrolysis (381, 389). The decade of haloether investigations (1968–1978) was reviewed in 1978 by Van Duuren (302), but the work did not stop there, and the experiences gained in previous years were used for further investigations concerning the carcinogenicity of halogenated olefinic and aliphatic hydrocarbons (306). In 1979, Albert et al (2) discussed an alert system for the identification of situations with high-level carcinogen exposure and suggested that such a system would be particularly effective if it focused primarily, but not exclusively, on nonsmokers. They pointed out that of the four lung cancer cases among young workers exposed to BCME, two involved nonsmokers.

Outside the United States, the development went more smoothly. Though there were quite a few BCME-related deaths, especially in the Federal Republic of Germany, they were not highlighted in such a dramatic way as in the United States, and the manufacturers concerned took the necessary measures as soon as the facts became known. The American point of view as regards BCME and CMME was generally adopted.

It seems as if BCME and CMME had not been regarded as so dangerous in Eastern Europe as in the Western world, at least in the period before and including 1977–1978. Zudová & Landa (346), in their paper about personnel monitoring by means of peripheral lymphocyte analysis, refer to BCME and CMME as "suspected carcinogens" and consider them as mutagens. In the Soviet Union the simultaneous use of formaldehyde and hydrochloric acid does not seem to have been regarded as dangerous, as judged by the paper of Tschegolja et al (297) of 1978. The authors described how flame-resistant fibers from phenol/formaldehyde resins were melt-spun from novolack resins and then cross-linked in baths containing 5–25 % of formaldehyde and 10–25 % of hydrochloric acid.

No relevant communications on BCME and/or CMME risks were found in the Czechoslovak, East German, Polish, and Soviet journals that were accessible during the preparation of the present document.

Attempts to establish direct contacts with persons and institutions in Czechoslovakia and the German Democratic Republic failed because the addressees did not answer the respective inquiries.

As regards Sweden, no original haloether research has so far been done. The occupational and hygienic aspects of haloethers and the respective developments abroad have, however, been closely followed.

In 1973 the Arbetarskyddsverket (355) and in 1979 the Arbetarskyddsstyrelsen (National Board of Occupational Safety and Health) (384) called attention to the risk of BCME. The 1978 list of the Swedish hygienic standards (Hygieniska gränsvärden, Arbetarskyddsstyrelsens anvisning nr 100) puts BCME, CMME and 10 other chemicals in a group for which the following regulation is valid:

The substances in question must neither be produced nor used in industry. This applies even to products in which these substances occur as impurities down to 0.1 weight-%. Even with contents under 0.1 weight-% measures must be taken to prevent exposure of workers [p 24].

Both haloethers, BCME and CMME, became targets of attention in several branches of industry where there was a possibility of formaldehyde reacting with chloride ions. The greatest attention was paid to them in the chemical and textile industries and in the field of formaldehyde disinfection (42, 54, 95). In other branches, the interest was only theoretical and no independent research was made. For example, in the food and cosmetics industries, only review articles were written (52, 65).

As regards the possibility of monitoring the health of workers exposed to haloethers, the present view is dim because the lung carcinomas due to haloethers are essentially an untreatable and rapidly fatal disease (329). A monitoring of the health of the workers would probably not be of much use (238, 244, 245, 246).

Need for further research

There are several areas that require further research concerning the BCME problem.

1. First of all the connection between formaldehyde and BCME as regards carcinogenicity must be clarified.

It is already known that lung cancer can be caused (i) by BCME alone, (ii) by a combination of formaldehyde and chloride ions, and (iii) by formaldehyde alone. The question is: Are the formaldehyde carcinogenicity, on one hand, and the BCME carcinogenicity, on the other, parts of the same problem, or are they two different and mutually independent phenomena?

If the formaldehyde carcinogenicity and the BCME carcinogenicity are only two sides of the same problem, then the causative mechanism must be established. Does formaldehyde act alone or as a precursor to BCME? Does BCME act alone or as a carrier of formaldehyde? As regards the second question, reference is made to the research results reported by Shooter in 1975 (260). (See the section on the carcinogenicity and mutagenicity of BCME in animals and cell systems.)

BCME is in fact an excellent solvent for fats and, as such, it would have no difficulties in penetrating cell membranes.

The present situation is, however, that there are about 70 documented cases of BCME-caused lung cancer in humans, while the carcinogenicity of formaldehyde has so far been shown only in animals (mostly rats). At present, there is nothing to indicate that formaldehyde is also carcinogenic in humans, in spite of heavy exposures of large numbers of people to this agent during the last 100 a or so. This situation would indicate that BCME carcinogenicity and formaldehyde carcinogenicity are two separate problems. In the first case, formaldehyde is one of the precursors of a very potent carcinogen, while in the second case it is suspected (but not proved) to be a human carcinogen. Thus the whole problem of formal-

dehyde, BCME, and their mutual relation will have to be studied in a complex way in the future.

2. The second question concerns what concentration of BCME in workroom air can be considered an acceptable risk.

3. It must be determined whether dangerous concentrations of BCME are formed in air from formaldehyde and chloride ions if the two are present in concentrations close to their respective hygienic standards.

4. Last, from the point of view of practical occupational and general hygiene, the following questions must be answered: (i) how much BCME can be formed in industrial processes that involve formaldehyde and chloride ions at the same time, (ii) how much BCME can be found in the workroom air if such processes are used, and (iii) can a possible BCME formation in the general atmosphere constitute a health risk for the population at large?

As regards the last question, there are indications that the lung cancer mortality in industrial regions can suddenly increase several times, with very short latency periods. BCME has one of the shortest latency periods as a carcinogen, and BCME precursors can very often be present in urban and industrial air. In such cases it is BCME that ought to be one of the prime suspects.

In 1979 Lloyd & Barclay (163) reported about such an increase of lung cancer mortality in an industrial community in Scotland in connection with a very short latency period. It has not yet been shown that the causative agent was BCME. The real cause is not yet known, and it is being investigated. It is, however, supposed that a cluster of BCME-caused lung cancers would present a similar picture.

Organization and experimental design for the present project

Formaldehyde-based resins are the most important industrial articles from which BCME might be released in manufacturing, hand-

ing, processing, and use. This is one reason why these resins were given priority.

The main targets were set as follows: (i) to

Table 4. Characteristics of the formaldehyde-based resins used.

Type of resin	Dry substance content (%)	Free formaldehyde content (weight-%)	Remarks
Urea/ formaldehyde	About 60	About 0.47	Contains a small amount of ammonia as hexamethylene tetramine
Melamine/ formaldehyde	About 50	About 0.17	Is modified with toluene sulfonamide and contains a small amount of methanol
Phenol/ formaldehyde	About 50	About 0.54	Contains a small amount of methanol

develop a safe method for testing formaldehyde-based resins as to BCME formation during their manufacture, handling, processing and use and (ii) to test the most important formaldehyde-based resins, ie, phenol/formaldehyde resins, urea/formaldehyde resins, and melamine/formaldehyde resins. These resins had to be of current commercial types.

The experimental work was planned and executed in four stages as mentioned in the Introduction.

The necessary laboratory equipment had to be designed and built according to the requirements of the research project in question, with special regard for the fact that a very dangerous and toxic substance was involved. Thus emphasis had to be placed on miniaturizing the equipment in order to produce and use only those quantities of BCME that were strictly needed for analytical purposes.

Another measure was to use disposable and inexpensive reaction vessels in which a possible BCME residue could be easily liquidated by the addition of a suitable agent.

Materials, equipment, and methods

The experimental design as regards the actual execution and evaluation of the experiments was as follows.

Materials

All chemicals used, with the exception of the gases, were Merck chemicals, of pro analysi

or pro synthesisi grades. The gases, chlorine 99.8 % and dry synthetic air containing 79 vol-% of nitrogen and 21 vol-% of oxygen, with water vapor content of ≤ 5 ppm, were from Messer, Griesheim.

The characteristics of the formaldehyde-based commercial-type resins used in the experiments are given in table 4.

Equipment

A large, heat-insulated, 120-l water bath was built. It could hold, submerged, either two reactors of 10 l each or four reactors of 1.4 l each (see fig 1 & 3).

The reactor vessels were made of borosilicate (Pyrex type) glass (Duran 50 – Schott Mainz – Jena glass), and they were equipped with massive screw-on Teflon lids. Each lid (see fig 2) carried a variable-speed electric motor for the agitator, an inlet and an outlet valve, a thermometer, and a septum arrangement for liquid and gas injection and for gas sample taking. The stirrer shaft and the propellers were made of Teflon as well. Inside the reactors, only glass and Teflon surfaces were exposed.

Each 10-l vessel (of which there were eight) was carried in a cage which allowed the round-bottomed glass vessels to stand upright. The reactor lids (of which there were two) could be screwed to the upper flanges of any of the reactor vessel cages.

Fig 1 shows two reactor vessels in their cages standing in front of the loaded water bath ready for operation.



Fig 1. Two 10-l reactors in operational condition on the water bath.

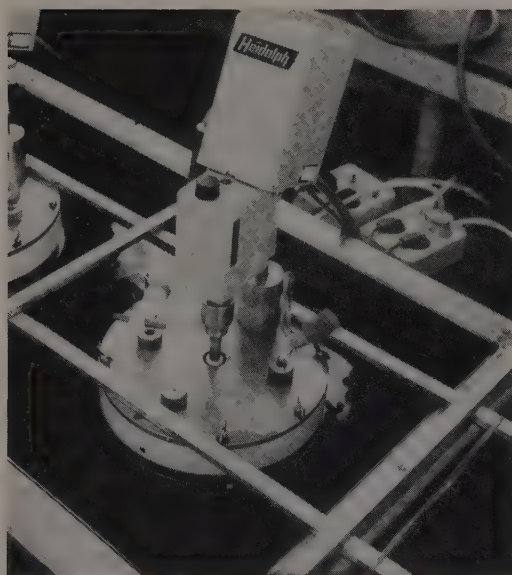


Fig 2. Lid of a 10-l reactor immersed in the water bath.

Fig 2 shows how the 10-l reactor vessels were held on the water bath by means of movable bars to control buoyancy.

The water bath had two magnetic stirrers for the heat-transferring water, an automatic temperature control, a heating arrangement allowing inputs of 1,000 to 5,000 W of electric energy, and a cooling arrangement in the form of a copper tube coil through which cold water could be circulated.

The reactors could be flushed and filled either with ambient air or with dry synthetic air. The volume of air fed through the reactors could be read off on a dry gas flow meter. With the use of a five-rotameter arrangement with four reactors on the water bath, each 1.4-l reactor could be fed a specified volume of ambient or dry synthetic air per unit of time. The rotameter system, mounted on the front edge of the water bath lid, is presented in fig 3 & 4. The rubber hose connections to the individual reactors are not shown.

Reactors containing BCME in air could be safely evacuated into the free atmosphere outside the building by means of a flexible plastic hose. The evacuation was done by pumping air through the inlet valve into the reactor, where it took along the BCME-containing air through the outlet valve into the evacuation hose.

Besides joint temperature control, the reactors were run individually. The water bath could operate at temperatures from 0°C to the boiling point of water. All experiments were performed at atmospheric or slightly increased pressure (because of gas expansion owing to increased temperature). The reactors were tested for leak- and suction-proofness at double the atmospheric pressure and at a vacuum of half the atmospheric pressure.

The 10-l reactors were used for BCME formation in the gaseous phase, while the 1.4-l reactors served for the liquid-phase experiments.

The arrangement of four reactors for the liquid-phase experiments is shown in fig 3 & 4. Fig 3 shows the water bath covered with a metal lid that carries four assembled reactors, while fig 4 shows the water bath with only one assembled reactor, one reactor vessel being half-drawn out of its respective opening and the remaining two reactor vessels sitting in their openings with their lids removed.

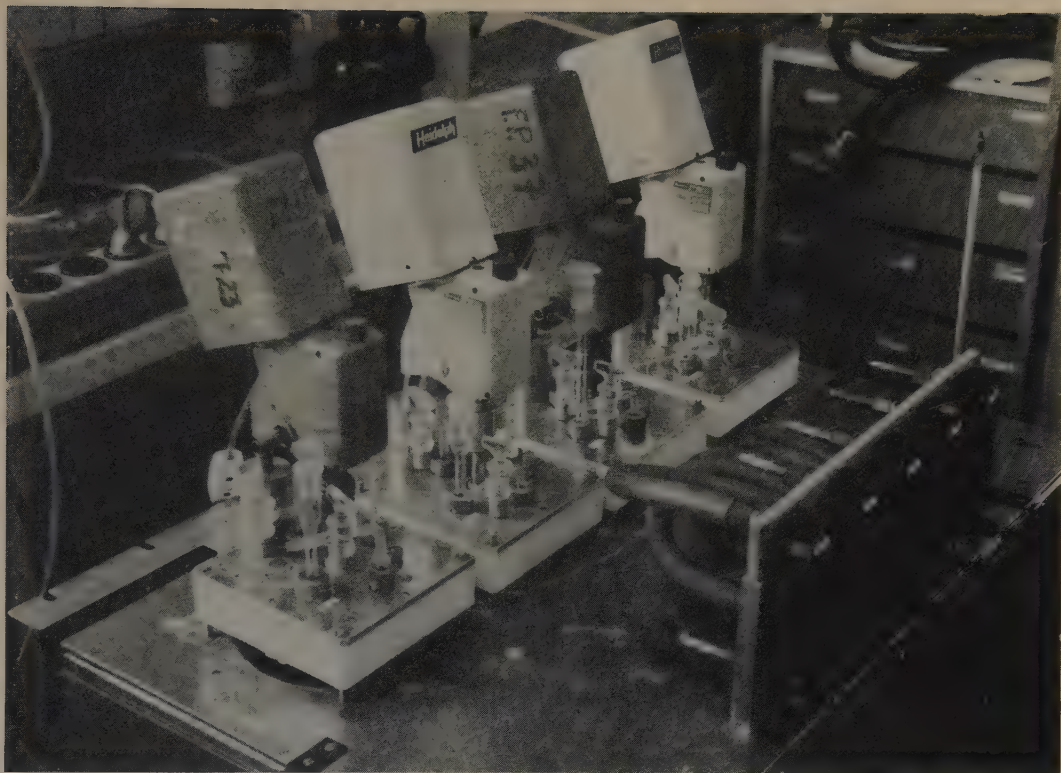


Fig 3. Four 1.4-l reactors in operational condition on the water bath.

In experiments concerning BCME destruction by means of condensing water, the 1.4-l reactors were used as gas reactors.

Fig 5 shows the reactor assembly used in these experiments. The reactor is heated by means of an electric resistance nest carried by a lift stage. Instead of heating, the reactor could be cooled by immersion in a large beak with water that could also be carried by the lift stage. In this arrangement the reactor lid also carries a two-point mercury temperature controller cooperating with a switch-on/switch-off relay for the heating nest.

The smaller lids of the 1.4-l reactors were designed in the same manner as the lids of the 10-l reactors. As the 1.4-l reactors were intended for work with liquids, their lids had stoppered inlets for metering funnels in addition to the usual complement consisting of an agitator motor, a gas inlet, a gas outlet, a septum arrangement, and a thermometer.

The 1.4-l reactor vessels had no cages; they were inserted into the respective openings in the water bath lid, where they hung by their flanges. The water bath lid carried four

bolts for each reactor for screwing together the reactor vessels and the reactor lid (see fig 4).

The agitator motors had variable-speed drives, but were used only at the speed of 100 r/min in both the gas and liquid reactors.

A special development of the present project was the so-called microreactor system in which vials with a 25-ml volume were used as reactors. These vials, made of potassium glass, were closed with Teflon caps and operated on two liquid baths, a water bath for temperatures up to 100°C and an oil bath for temperatures up to 200°C.

The length of the vials was 75 mm, their diameter was 23 mm, and their neck opening had a diameter of 20/12 mm. They were the "Ampullen N 20-20", from Messrs Macherey-Nagel & Co, D-516 Düren, and they were used with "Bördelkappen N 20 TB" Teflon caps. Fig 6 shows the vials and their caps.

Each bath had a metallic vessel of rectangular shape that contained about 30 l of the respective heat transfer medium. The baths

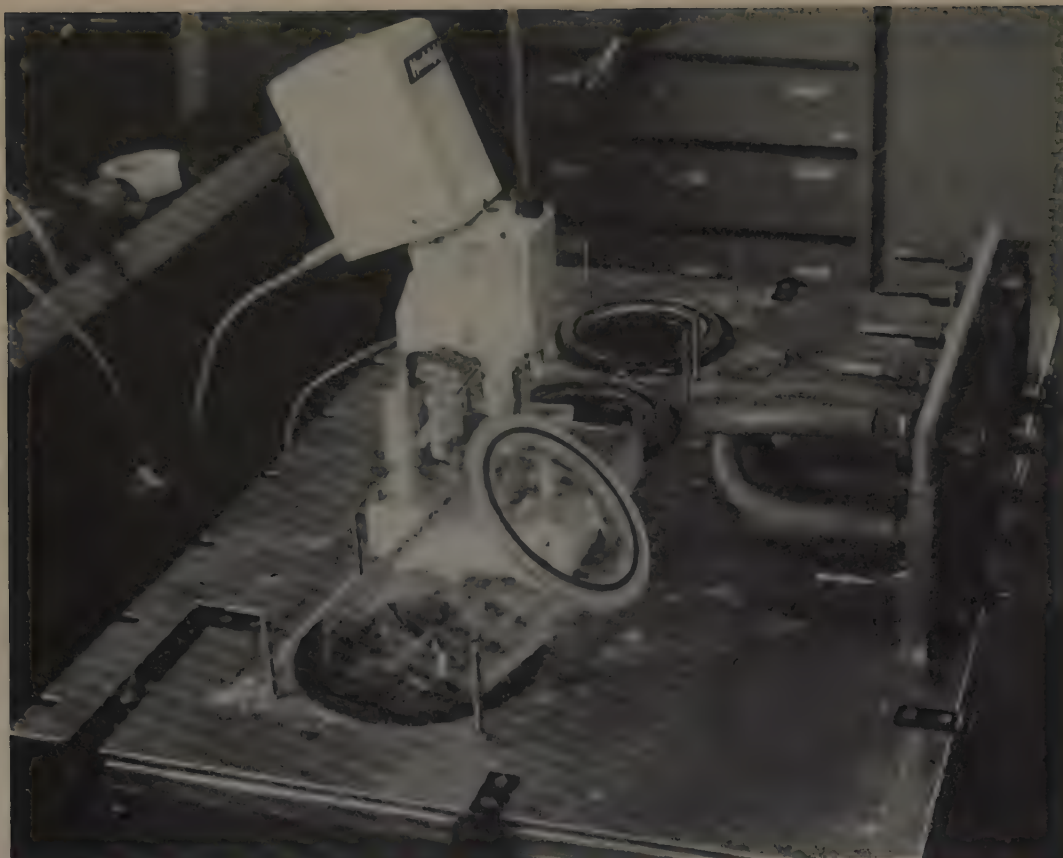


Fig 4. Water bath with four 1.4-l reactors being assembled.

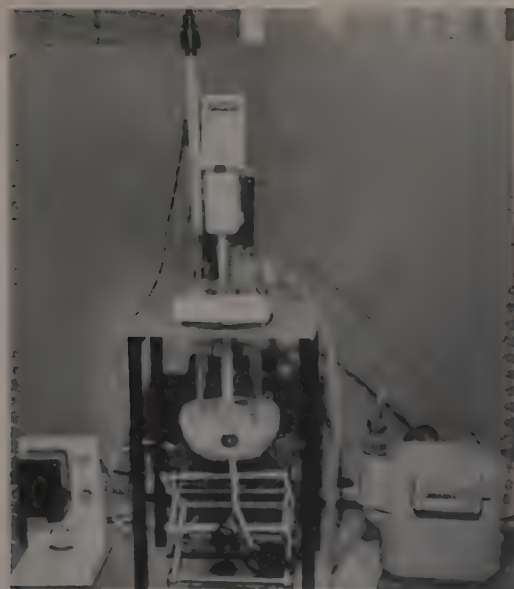


Fig 5. Gas reactor assembly for bis(chloromethyl)ether mopping-up tests.

had two-point mercury temperature controls, as well as mercury thermometers for checking purposes.

Fig 7 shows the water bath (empty) and fig 8 the oil bath with the large carrier plate fitted with vial holders.

The vial holders consisted of two parts (see fig 9). The shorter parts were hard-soldered to the undersides of the carrier plates, while the longer lower parts could be snapped into the upper parts by means of bayonet locks. Fig 9 shows a small carrier plate for four vial holders.

There were, on the whole, four small carrier plates, each for four vial holders, and a large carrier plate for $6 \times 4 = 24$ vial holders per bath (see fig 10). Thus each bath could carry up to 40 vial holders, and therefore up to 40 microreactors could be run at the same time on one bath.

The lower parts of the vial holders (see fig 9) were 87.5 mm long, made of brass tubing, 27/29 mm in diameter, and provided with sol-



Fig 6. Vials and caps for the microreactors.

dered-on bottoms of brass plate with holes, 10 mm in diameter, in the middle of the bottoms. The mantle of each lower part had 4×8 holes, 5 mm in diameter, in axial rows.

The upper parts, connected to the carrier plates, were slightly larger in diameter and had two L-shaped grooves each that were positioned opposite each other for the pins of the lower parts to register with for bayonet locking.

During the loading of a vial holder (see fig 9), a compression spring, 23 mm high and 21 mm in diameter with five turns of wire, was first sunk into the lower part of the hol-

der. Then the capped vial containing the gaseous, liquid, or solid reactants was inserted, and the lower part of the holder, with the spring and the vial, was snapped into the respective upper part. The spring action pressed the upper surface of the Teflon cap (with the middle disc removed – see fig 6) onto a hole, 3 mm in diameter, in the brass carrier plate, 3 mm thick. Through this hole, the vial was accessible to the syringe needle. The heat transfer liquid reached up to the bottom surfaces of the carrier plates, with the consequence that the top surfaces of the carrier plates were kept clean so that the

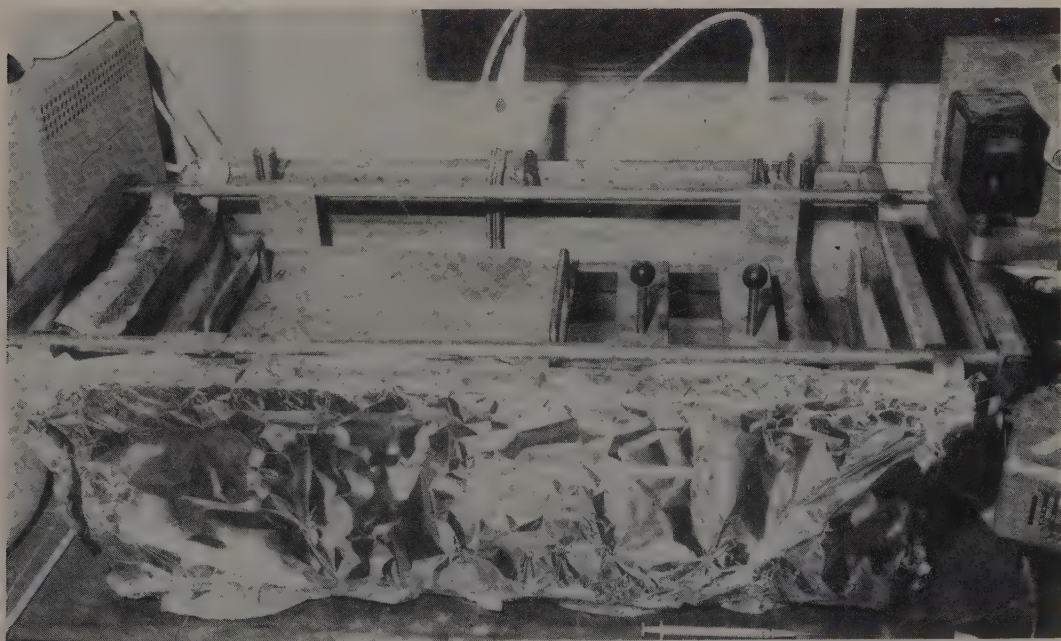


Fig 7. Water bath with reciprocating carriage for the vial microreactors.

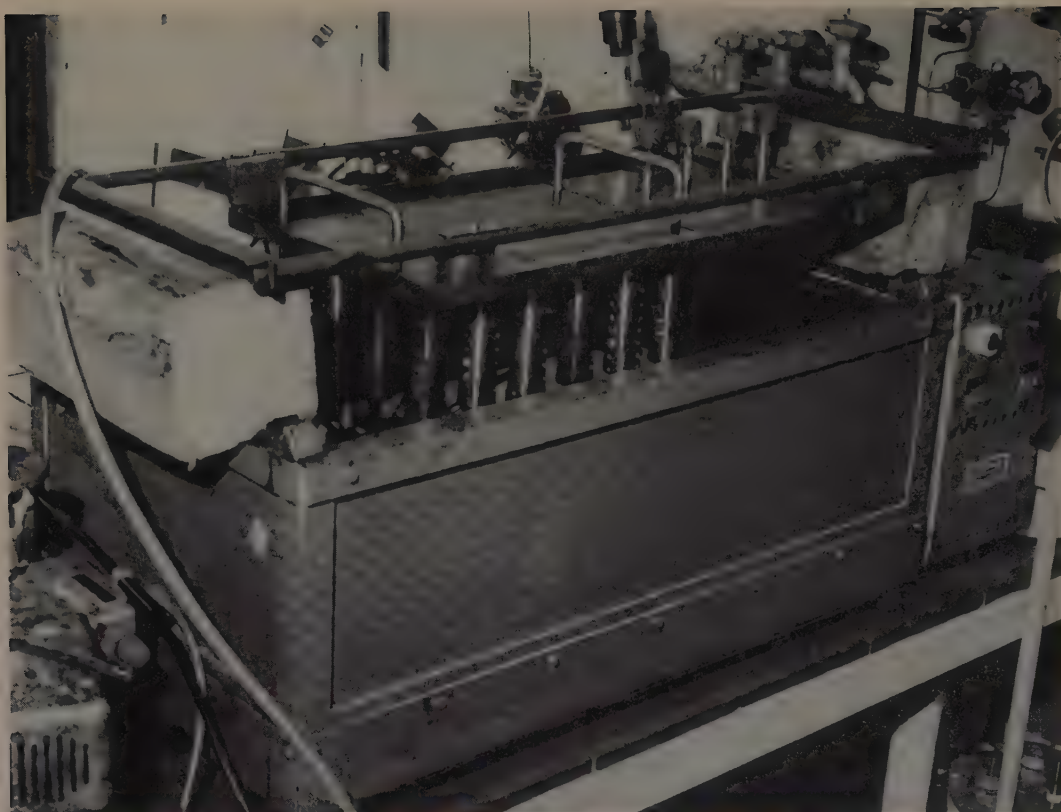


Fig 8. Oil bath with lifted carriage being prepared for the experiments.

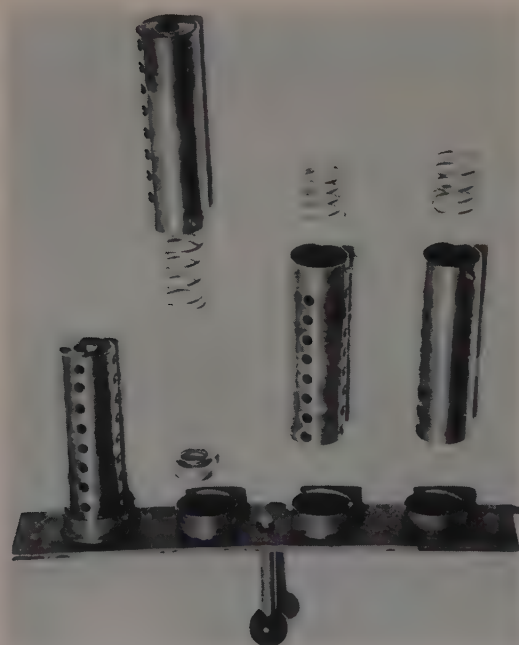


Fig 9. Narrow carrier plate with vial holders.

syringe needles did not become contaminated.

The carrier plates, with the vial holders attached underneath, were suspended from reciprocating frames (carriages), which were moved to and fro by variable-speed electric motors. The reciprocating frame arrangement can be seen in fig 7 in its operational position, while in fig 8 the reciprocating frame is seen resting on two wood blocks, which was the arrangement used for the loading of the bath in the experiments.

The microreactor system performed to full satisfaction. The baths were easy to load for the experiments, and the reciprocating perforated vial holders facilitated the heat transfer between the bath liquid and the microreactors, while at the same time protecting the adjacent vials from chain reaction explosions in case one vial burst.

Equipment surfaces. The materials coming in contact with BCME play an important role in that BCME, being highly reactive, is ex-



Fig 10. System of carrier plates for either the water bath or the oil bath (total capacity 40 vials).

tremely sensitive to the impurities and to the character of the surfaces.

In experiments with BCME, a correct way must be found to clean the surfaces of the experimental equipment that come in contact with BCME. Unfortunately, a surface treatment that is suitable for one type of material can be absolutely wrong for another type of material. For the purpose of the present investigation, two basic treatments were developed for glass and Teflon surfaces that came in contact with BCME within the reactors. They are presented in table 5.

The Teflon surfaces were always treated "normally," while the "special" treatment had to be used for the borosilicate glass. The

potassium glass of the microreactor vials was treated "normally" as well. For the sake of comparison some experiments were made with untreated potassium glass vials.

If, for example, the microreactors were "specially" treated, their inside surfaces made the gaseous BCME rapidly disappear from the gas phase. The same happened if reactors from borosilicate glass were "normally" treated.

Thus there proved to be no universal way of treating glass surfaces that had to come in contact with BCME. Even if the glass surfaces are cleaned correctly, it can happen that none or too little BCME will form from formaldehyde and chloride ions or that the injected BCME will disappear within the glass vessel.

These occurrences must, however, by no means be interpreted as negative results when they happen for the first time. The experiments must be repeated several times, because there is always a definite possibility that something has gone wrong. BCME is very elusive, and it is supposed that quite a few results obtained in the past were due to this disappearance of BCME owing to uncontrollable influences. Thus the disappearance of BCME is a multifactorial phenomenon.

As a consequence, checking and calibrating with pure BCME (usually in solution in an inert solvent) must continue throughout the experiment in order to determine whether the respective experimental arrangement destroys the BCME that is formed and – if it does – how much BCME survives.

Table 5. Degrees of cleaning treatment for laboratory glass.

Degree of treatment	Operations
Special treatment	1. Rinsing with sodium hydroxide 1 N 2. Rinsing with distilled water 3. Rinsing with chromic acid 4. Rinsing with distilled water 5. Rinsing with 100 % methanol 6. Rinsing with distilled water 7. Heat treatment at 250°C for 24 h 8. Cooling down 9. Blowing out with dry artificial air
Normal treatment	1. Rinsing with 100 % methanol 2. Rinsing with distilled water 3. Drying at 105°C 4. Cooling down
No treatment	Using the laboratory glass in the state in which it was delivered

Table 6. Operational conditions for the gas chromatography-mass spectroscopy system used. Equipment: Finnigan Model F 3100 mass spectrometer coupled to a Finnigan Model 9500 gas chromatograph over a Finnigan allglas jet separator. Procedure: Mass determination and single-ion detection at $m/e=79$.

Conditions	Values
Gas chromatograph	
Column, packed	Glass, 2.5 m $\times$ 2 mm internal diameter, packed with 4 % Carbowax 20 Mon Chromosorb NAW 80/100 mesh
Oven temperature	80 or 100°C
Injection port temperature	150°C
Separator and transfer line temperature	150°C
Helium flow	30 ml/min
Retention time	Approximately 6 min at 80°C Approximately 3 min 15 s at 100°C
Mass spectrometer	
Electron energy	67 eV
Emission	0.4 mA
Collector	0.32 mV
Ionizer volume	0.09 mA
Ion energy	5.2 V
Extractor	3.5 V
Collector	36 V
Lens	-27 V
Multiplier voltage	1,350 V
Detection limit	Approximately 14 ng/l or 7 pg/500 μ l for signal-to-noise ratio of 3:1

Many materials must be avoided in experiments with BCME, especially if low concentrations of gaseous BCME are used or formed. Cellulose-containing materials, rubbers, many metals, many plastics, water, water-containing materials, etc, will decompose BCME in an uncontrollable way, sometimes leaving no trace at all of the compound. Even absorption-release phenomena might occur in the case of rubber (eg, in closures) and BCME, as they do in the case of rubber and, eg, methane, ethane, and acetylene (146).

Methods

The direct gas chromatographic-mass spectroscopic method without enrichment, which was used in the present investigation, is very selective, but not so sensitive as methods working with adsorbents, owing to the fact that maximum practical gas volumes, which can be injected into the gas chromatographic-mass spectroscopic setup, are of the order of 0.5 to 1.0 ml, while adsorbent-based

methods can collect BCME from several liters of air. But the direct gas chromatographic-mass spectroscopic method is eminently suitable for quickly repeated analyses and allows a large number of analytical determinations to be made during a workday.

The apparatus and work conditions that were used are described in table 6, while the respective calibration procedure is reviewed in table 7.

In the determination of BCME by the gas chromatographic-mass spectroscopic method, the single-ion procedure at $m/e=79$ was used. The peak at $m/e=79$, as well as its concomitant twin peak at $m/e=81$, belong to the $C_2H_4OCl^+$ ion.

For checking purposes there is another pair of peaks available, namely $m/e=49$ and 51.

The occurrence of the peak pairs 79/81 and 49/51 (the latter for the CH_2Cl^+ ion) is due to there being two chlorine isotopes, namely, chlorine ^{35}Cl and ^{37}Cl , respectively, with a quantitative ratio of about 3 : 1.

The spectrum in fig 11, valid for the *Finni-*

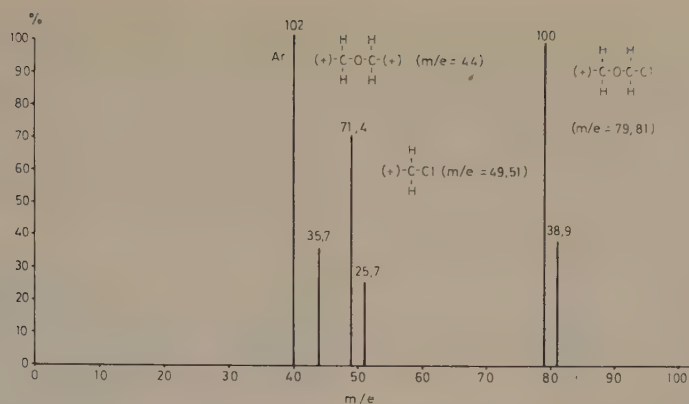
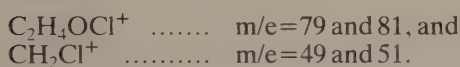


Fig 11. Mass spectrographic spectrum of bis(chloromethyl)ether. (Column: 4 % Chromosorb NAW 80/100 mesh, 80°). Natural chlorine isotope ratio: $^{35}\text{Cl} : ^{37}\text{Cl} = 75.4 : 24.6$, m/e values for ^{35}Cl : 44, 49, 79; m/e values for ^{37}Cl : 51, 81.

gan gas chromatographic-mass spectroscopic setup used, shows both peaks for the frag-ments



There is, besides, an unimportant peak at $m/e=44$ (the corresponding twin of which at $m/e=46$ is not shown).

The peaks $m/e=79$ and $m/e=49$ are the highest, and they are completely sufficient for identifying BCME. Frankel et al (92) reported that, among the 8,782 compounds studied by Heller in 1971, there was only one compound, namely BCME, that met the requirement of having its major peak at $m/e=79$ and a second peak at $m/e=49$, the latter possessing at least one-third of the intensity of the major peak.

Table 7. Determination of the bis(chloromethyl)ether content in the gas being investigated.

Operation	Procedure
Determination of the value of a	At the sensitivity of 10^{-7} of the gas chromatography-mass spectrometry setup, $1 \mu\text{l}$ of the BCME 10^{-6} solution in dichloromethane is injected, which results in a peak of a scale divisions on the writeout diagram paper. The concentration of BCME at this sensitivity and with an injection of 0.5 ml of the gas being investigated is calculated as 0.56/a ppm of BCME per scale division.
Operational checks of the value of a	At the beginning of the measurements, the first value of a is determined from the use of at least five injections of the BCME solution. During the measurements checks with the same BCME solution are made at least every hour or after 10–12 gas injections in order to determine whether and how the value of a has changed. If the difference is greater than $\pm 10\%$, a new value of a must be determined with the use of at least three injections of the BCME solution.

When there were doubts about whether the peak $m/e=79$ was BCME or not, a multi-ion analysis was run. If there was a peak at $m/e=49$ that complied with the above requirement, then it was accepted that the peak $m/e=79$ in question belonged to BCME.

The sensitivity of analysis in the present investigation was about 3 ppb of BCME in air (corresponding to about 14 ng/l or 7 pg/0.5 ml injection).

With BCME, one volume part per billion corresponds to 4.7 ng/l of air, as calculated from the ideal gas law.

For the present investigation, the *Finnigan* gas chromatography-mass spectroscopy setup was located in the immediate vicinity of the BCME-developing reactors from which gas samples of 10 to 500 μ l were taken and immediately injected through the septum into the entry port of the gas chromatograph.

The $m/e=79$ fragment was currently monitored in the single-ion procedure, and peaks corresponding to the respective retention time were looked for and marked off in the spectrum being drawn on the chart of the writeout.

The BCME concentrations were calculated from the peak heights and the preset sensitivity of the gas chromatography-mass spectroscopy setup. Checks with pure BCME were run according to table 7.

In a small number of experiments a speeded-up method of gas chromatographic-mass spectroscopic analysis was tentatively used. It was the so-called "multiple-shot procedure," which is described under "Experimental procedure" in the section dealing with the BCME formation experiments in the gaseous phase.

Experiments and results

On the whole, four stages of experiments were performed:

- a BCME formation in the gaseous phase,
- b BCME formation in the liquid phase,
- c BCME formation in the solid phase, and
- d BCME destruction in the gaseous phase.

These stages can be shortly characterized as follows:

- a The experiments investigating the formation of BCME in the gaseous phase from its

precursors formaldehyde and hydrogen chloride were meant as introductory experiments with which to get acquainted with the substance in question, its properties and behavior. Conventional equipment was used in most of these experiments, and their results are in agreement with those of earlier experiments by other authors.

- b The experiments investigating the formation of BCME in the liquid phase were based on an original experimental design, while the equipment was partly conventional and partly of special construction.

- c Experiments in relatively high-volume gas reactors, used in stages a and b, in which dangerously large amounts of BCME could be formed, presented a danger of BCME leakage into the laboratory air, both during unattended operation and during reactor servicing. Therefore, ways and means were looked for which could eliminate or, at least, greatly reduce this danger and, if possible, increase experiment productivity, which was considered low in work with large volume reactors. For this purpose, the "microreactor method" was developed. This method considerably increased the productivity of experimenting and allowed safe work. The microreactor method was not only used in the stage c experiments (all of which were performed in this way), but also in stages a and b in order to obtain supplementary information.

- d The experiments investigating the destruction of BCME in the gaseous phase were not planned beforehand. During the experiments of stages a through c it became evident that condensing water vapor was an efficient BCME scavenger. Owing to the practical importance of this phenomenon, the decision was made to study it in greater detail.

Bis(chloromethyl)ether formation experiments in the gaseous phase

The purpose of the stage a experiments was to study the formation of BCME from its precursors in the gaseous phase.

Experimental procedure. The experiments were performed in 10-l glass reactors, alternating eight glass reactor vessels held in special cages with two Teflon lids.

The reactants, formaldehyde and hydrogen chloride, were added to the reactors as a

Table 8. Results of the bis(chloromethyl)ether (BCME) forming experiments in the gaseous phase in comparison with Frankel et al's results (92).

Results	Reactant concentrations (ppm)			Experimental conditions		Resultant concentration of BCME (ppm) in air	Calculated values of equilibrium constants (l/mol) ²		
	Form- aldehyde	Hydrogen chloride	Water vapor	Temperature			Relative humidity (%)	K ₁ ^a	K ₂ ^b
				Degree	Kelvins				
Present investiga- tion	400	400	2,700	66	339	1	1.1×10 ⁻¹	9.0×10 ⁶	3.7×10 ²
	400	800	4,000	98	371	1	2.2×10 ⁻¹	8.0×10 ⁶	4.4×10 ²
	800	400	3,900	97	370	1	3.8×10 ⁻¹	1.3×10 ⁷	1.3×10 ³
	800	800	5,300	21	294	22	2.7×10 ⁻¹	2.0×10 ⁶	1.0×10 ²
	2,000	2,000	13,300	20	293	58	38	1.8×10 ⁷	5.2×10 ⁴
	4,000	4,000	26,600	58	331	17	23	1.8×10 ⁶	1.5×10 ³
Frankel etal (92)	20	20	13,300	26	299	40	5.0×10 ⁻⁴	2.5×10 ¹⁰	9.4×10 ²
	100	100	13,300	26	299	40	3.0×10 ⁻³	2.4×10 ⁸	5.4×10 ¹
	300	300	13,300	26	299	40	2.3×10 ⁻²	2.3×10 ⁷	3.9×10 ¹
	1,000	1,000	13,300	26	299	40	1.3×10 ⁻¹	1.0×10 ⁶	1.0×10 ¹
	1,000	10,000	13,300	26	299	40	7.3×10 ⁻¹	5.9×10 ⁴	3.2×10 ⁰
	4,000	40,000	13,300	26	299	40	5	1.6×10 ³	5.9×10 ¹

^a Equilibrium constants K₁ were calculated with the atmospheric moisture being considered.

^b Equilibrium constants K₂ were calculated with the atmospheric moisture not being considered.

35 % aqueous solution of formaldehyde, stabilized with about 10 % of methanol, and 37 % hydrochloric acid. The reactants were added by means of a metering syringe, the hollow needle of which penetrated the septum in the reactor lid.

The reactants being in solution, a certain amount of water was added to the atmosphere of dry artificial air inside the reactors, which resulted in a certain percentage of relative humidity at the respective temperature.

The operating procedure was as follows: (i) flushing the assembled air-tight reactor with dry air and, eventually, filling it with the same; (ii) adjusting the temperature of the enclosed air to the starting value; (iii) injecting the calculated amount of formaldehyde solution and hydrochloric acid; (iv) waiting for about 60 min; and (v) taking the first sample of air out of the reactor and analyzing it on the gas chromatography-mass spectroscopy setup.

During the 60-min waiting period the gas chromatography-mass spectroscopy setup was being prepared for measurements by a warm-up and several injections of the calibrating BCME solution, used to determine the initial value of *a* (see table 7).

Thereafter, the temperature of the reactors was increased or decreased and samples

of BCME-containing air were continuously taken out of the reactor and analyzed as specified by the respective experimental design.

Table 8 shows the results of the BCME-forming experiments, as compared with those of Frankel et al (92).

It can be seen that the present experiments produced higher BCME concentrations. Both experimental series are, however, entirely consistent, the difference between them being due to the fact that Frankel et al's experiments reflect average values while in the present ones maximum values of BCME concentrations were looked for.

Fig 12 shows the formation of a BCME concentration maximum in a system involving 4,000 ppm of formaldehyde, 4,000 ppm of hydrogen chloride, and 26,000 ppm of water vapor. It can be seen that the exact points of the maximum values of BCME concentration can be elusive, as the BCME concentrations can vary a great deal between subsequent measurements performed at different temperatures and relative humidities of the air.

In order to determine the dependence of the BCME concentrations on small differences in temperature and/or relative humidity, a measurement was made in a system involving 2,000 ppm of formaldehyde,

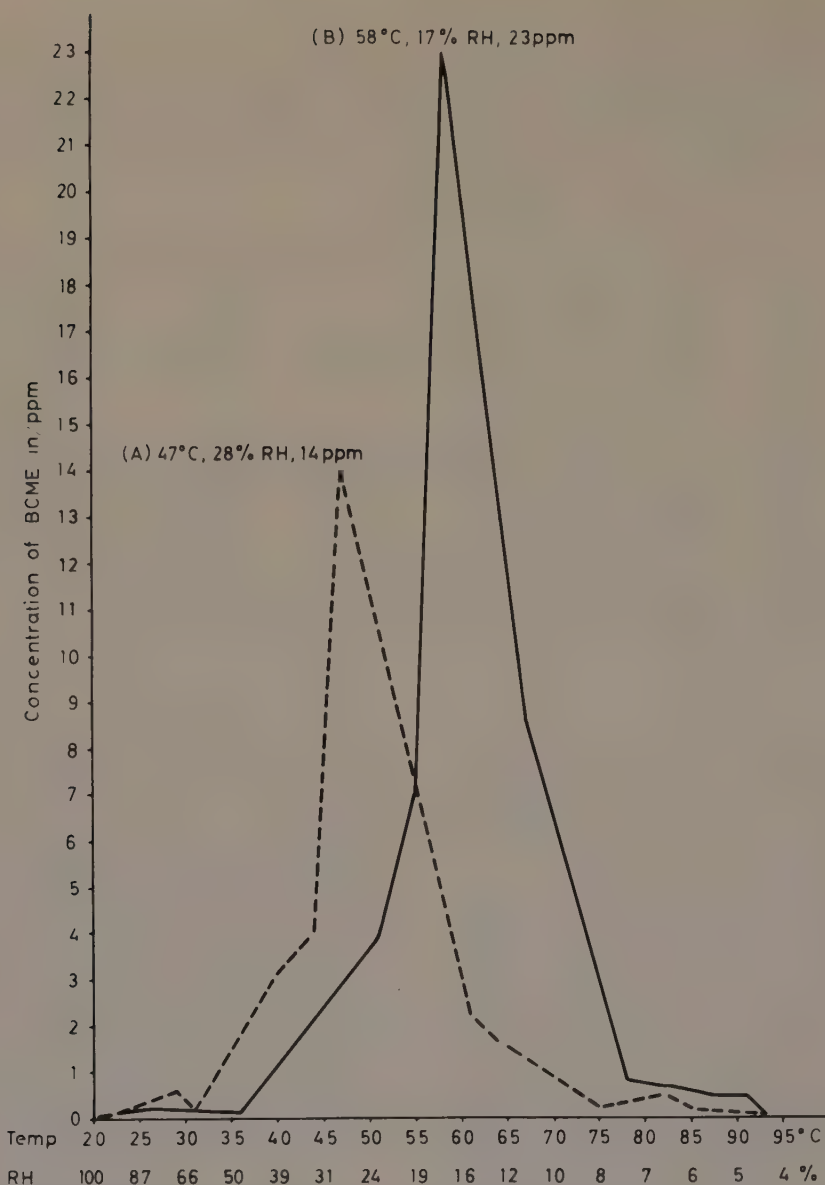


Fig 12. Formation of bis(chloromethyl)ether (BCME) in two closed systems operated simultaneously on the same water bath, as dependent on the temperature (Temp) and/or relative humidity (RH) of the air. The reaction system contained 4,000 ppm of formaldehyde, 4,000 ppm of hydrogen chloride, and 26,600 ppm of water vapor.

2,000 ppm of hydrogen chloride, and 13,300 ppm of water vapor. Fig 13 shows that the BCME concentration can vary over several orders of magnitude in very small intervals of temperature and/or relative humidity.

These oscillations seem to remind one of the dissipative structures of the Belousov–Zhabotinskij type. In the nonequilibrium

thermodynamics even nonperiodic, “chaotic” oscillations are possible. Any future research in the field of BCME formation will have to pay attention to these oscillations, provided they really exist and are not a consequence of the experimental design used in the present experiments.

In order to perform the analyses at a more rapid rate than the respective retention time

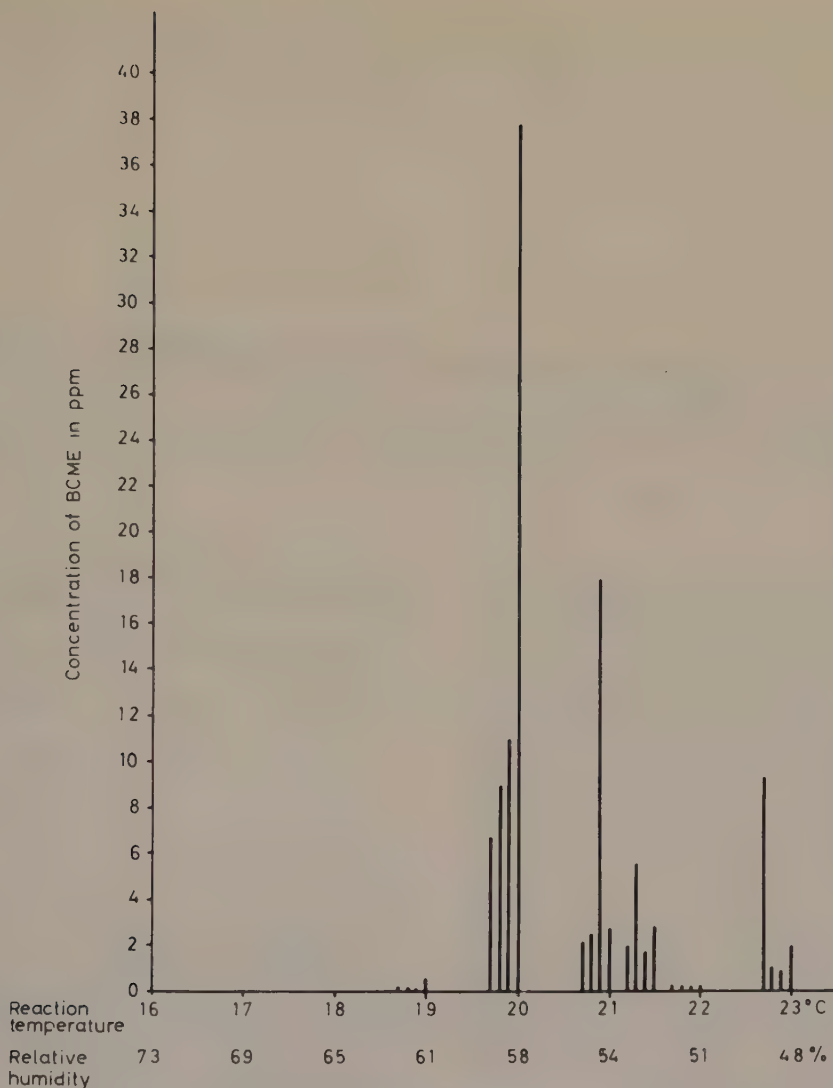


Fig 13. Formation of bis(chloromethyl)ether (BCME) in a closed system, as dependent on the temperature and/or relative humidity of the air. The reaction system contained 2,000 ppm of formaldehyde, 2,000 ppm of hydrogen chloride, and 13,300 ppm of water vapor.

on the gas chromatography-mass spectroscopy setup allowed, a new method, the so-called “multiple-shot procedure,” was tried. The principle of this procedure is not to wait with the next injection until the retention time expires, but to go on injecting the BCME-containing air samples at 1-min intervals; thus as many as four separate BCME zones pass through the gas chromatograph column at the same time.

In this way, it was possible to analyze the BCME-containing air at temperature

changes of a few tenths of a degree Celsius. This procedure could be adopted with the simple formaldehyde/hydrogen chloride/water system, as there were no “trailing peaks” of unknown compounds which could interfere with the BCME peaks following closely after each other.

As regards the effect of water content in the air upon the reaction of BCME formation and decomposition, no consistent responses were obtained. Theoretically, an addition of water into the system BCME/

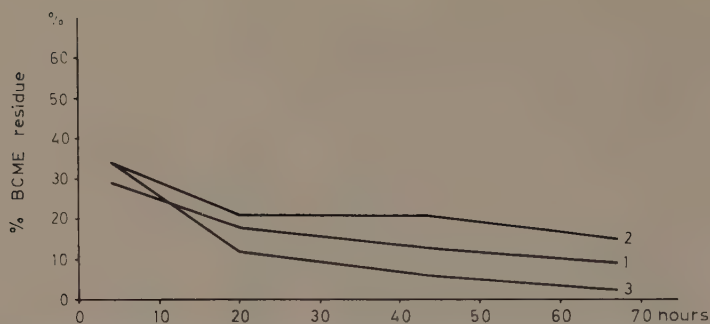


Fig 14. Effect of excess hydrogen chloride and formaldehyde on the disappearance of bis(chloromethyl)ether (BCME) in air. The experiments were performed in 25-ml glass vials, at 25°C, in daylight. Initial injections at time $t=0$, into air with 50 % relative humidity:

curve 1 – only 6 ppm of BCME; curve 2 – 6 ppm of BCME+0.5 ml of headspace gases from a 1-l bottle with 35 % formaldehyde solution in water; curve 3 – 6 ppm of BCME+0.5 ml of headspace gases from a 1-l bottle with 37 % hydrochloric acid.

formaldehyde/hydrogen chloride/water/air ought to decrease the concentration of BCME. When such experiments were made, an addition of water vapor into these systems either increased or decreased or kept constant the concentration of BCME. No explanation for this phenomenon can be offered.

The effect of temperature on the rate of BCME decomposition in air saturated with water vapor was considerable though an even greater effect could have been expected, theoretically.

The fact that the reaction half-time of BCME decomposition decreases with increasing BCME content in the reaction system can be interpreted as an autocatalytic effect. The respective half-times of BCME hydrolysis at two temperatures (60° and 80°C) can be seen in table 9.

Table 9. Reaction half-times for the hydrolysis of bis(chloromethyl)ether in air at 100 % relative humidity.

Initial concentration (ppm)	Temperature (°C)	Reaction half-time	
		Minutes	Hours
0.28	60	1,200	20
	80	600	10
1.4	60	720	12
	80	360	6

When BCME-containing air was enriched with gaseous formaldehyde, on one hand, and with gaseous hydrogen chloride, on the other, it was found that formaldehyde delayed the spontaneous disappearance of BCME in air, while hydrogen chloride accelerated it (fig 14).

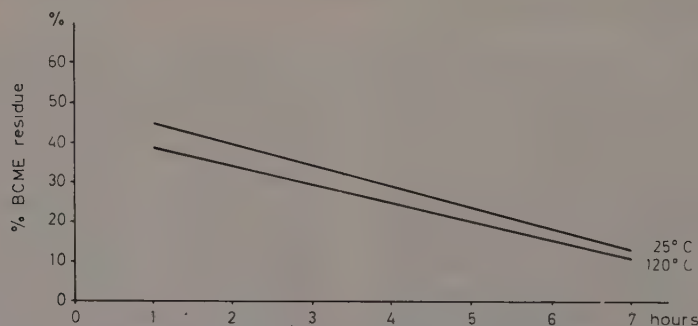


Fig 15. Disappearance rate of bis(chloromethyl)ether (BCME) in air, as dependent on temperature and reaction time. The experiments were performed in 25-ml glass vials on the oil bath. Initial injections of 1.2 ppm of BCME, at time $t=0$, into air with 50 % relative humidity. The following linear equations were derived:

$$c_{\text{BCME}}^{25} (\%) = 50.32 - 5.37t; c_{\text{BCME}}^{120} (\%) = 43.48 - 4.67t; (t = \text{time in hours}).$$

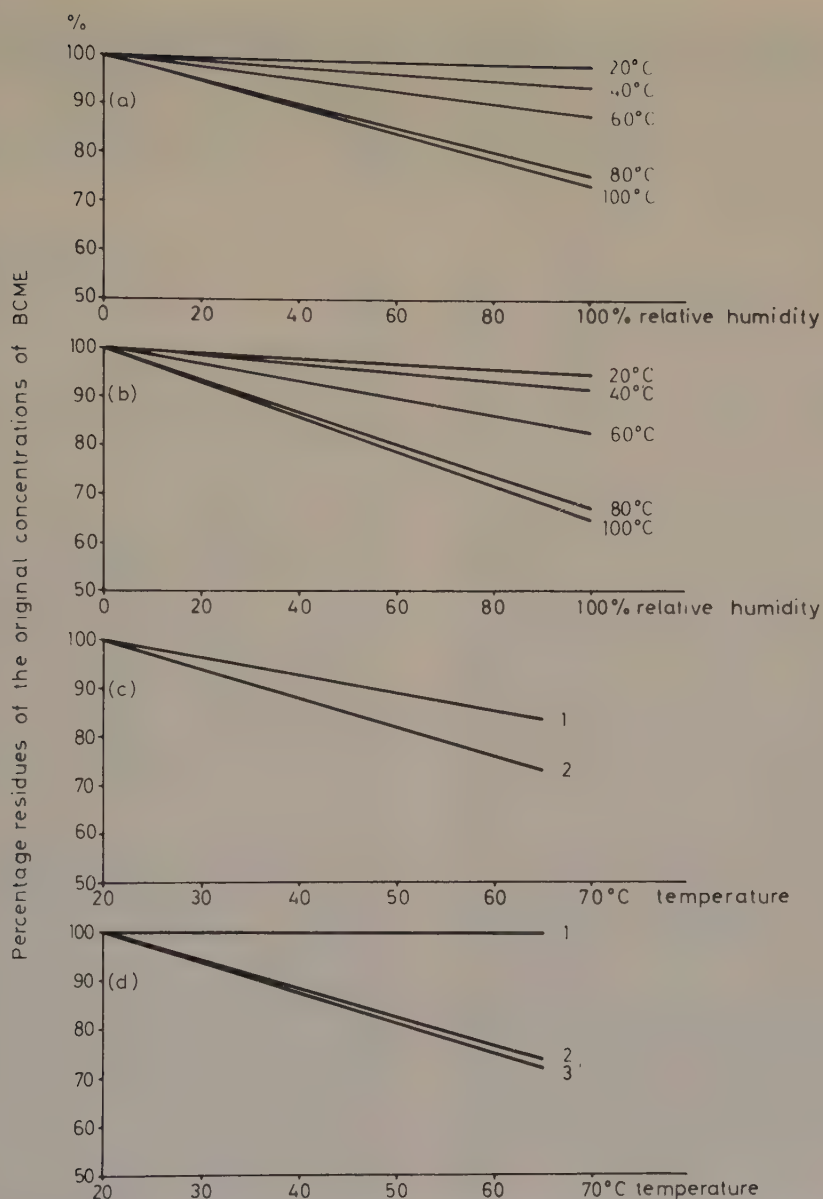


Fig 16. Disappearance of bis(chloromethyl)ether (BCME), as dependent on the relative humidity at different temperatures and on the initial concentration, temperature, and type of accompanying vapors. The experiments were performed in 1.4-l reactors.

(a) BCME input 0.28 ppm; (b) BCME input 1.4 ppm;

(c) BCME added to dry air: 1 – initial concentration of 8.4 ppm and 2 – initial concentration of 2.8 ppm;

(d) initial concentration of 2.8 ppm of BCME: 1 – together with 13,400 ppm of water vapor, 2 – together with 22,800 ppm of n-hexane vapor, and 3 – in dry air.

When the thermal decomposition of BCME in air was studied, it was found that the function

$$c_{\text{BCME}}(\%) = f(t)_{T=\text{const}} \quad (\text{eq 4})$$

was linear, having the form of

$$c_{\text{BCME}}(\%) = a - b \cdot t \quad (\text{eq 5})$$

where t = time in hours, T = temperature in degrees Celsius and a and b = constants.

Table 10. Disappearance of bis(chloromethyl)ether (BCME) in air-filled glass reactors because of adsorption and/or decomposition phenomena. (Reactor material: 25-ml reactors from potassium glass, 1,400-ml reactors from Pyrex type glass; in the small reactors the contents were not stirred, in the large reactors they were continuously stirred at 100 r/min; volume ratio: $V_{1400} : V_{25} = 56 : 1$, surface ratio: $S_{1400} : V_{25} = 15 : 1$).

Reactor volume (ml)	Input of BCME (ppm)	Temperature (°C)	Reaction time (min)	BCME residue (%)	BCME loss (%)
25	0.12	20	152	52	48
25	1.2	25	68	41	59
25	1.2	25	178	38	62
25	6.0	20	157	35	65
25	6.0	20	240	29	71
25	24	20	167	20	80
1,400	0.71	25	65	34	66
1,400	1.0	25	27	33	67

These (probably only seemingly) linear functions could, however, be formulated only for temperatures of 25 and 120°C. At 180°C the values spread too much and too irregularly to allow an assessment (fig 15).

Control experiments were made in order to ascertain whether BCME could be formed from its precursors on the filling of the gas chromatograph column while these reactants passed through it after simultaneous or delayed injections. Only very low concentrations of BCME were found with simultaneous injections of high concentrations of formaldehyde and hydrogen chloride in air. When the reactants were injected separately, first the one and then the other and vice versa, with delays of up to 30 s, no BCME formation was determined.

Fig 16 shows the decomposition of BCME in air as dependent on temperature, relative humidity, and BCME input concentration. Furthermore it shows the behavior of BCME in dry air and in the presence of n-hexane

vapor, as compared with water vapor. The reaction times for each relative humidity and temperature step were 30 min. Fig 16d points to a BCME-protecting behavior of water vapor, as compared with dry air containing n-hexane vapor. This seems to be another example of an apparently inconsistent behavior on the part of BCME.

This disappearance of BCME in air-filled glass reactors was studied in vessels having volumes of 25 ml and 1,400 ml, respectively. The results are shown in table 10.

Of special interest is the increasing percentage loss of BCME in air with an increasing input concentration of BCME in 25-ml reactors.

In order to investigate a potential surface and/or autocatalytic effect on the disappearance of BCME at various concentrations in the same amount of air, an experiment was made in which normally treated glass vials filled with ambient air were injected with various concentrations of BCME and then kept at 25°C. The results are summed up in table 11. They show a surface and/or autocatalytic effect (probably due to released hydrogen chloride). The following exponential equation could be established (with a coefficient of determination equal to $r^2 = 1.00$).

$$c_{\text{out}}(\%) = 44.01 \times e^{-0.389 \cdot c_{\text{in}}(\text{ppm})} \quad (\text{eq } 6)$$

where $c_{\text{out}}(\%)$ is the BCME output concentration in percent of the input and $c_{\text{in}}(\text{ppm})$ is the BCME input concentration (original injection) in parts per million.

Besides, vials containing 36 cm² of high-purity cellulosic filter paper each in ambient air were injected with 6 to 120 ppm of

Table 11. Spontaneous disappearance of bis(chloromethyl)ether in 25-ml glass reactors at 25°C, as dependent on the amount of original input.

Input (ppm)	Reaction time (min)	Residual content (%)	Disappeared amount (%)
1.2	176	38	62
2.4	199	36	64
6.0	213	37	63
12	234	32	68
24	248	18	82
60	262	4.2	> 95
120	276	0.41	> 99

BCME. The results after a reaction time of 300 min were > 98 % of decomposed BCME with a 6 ppm input and > 99 % of decomposed BCME with inputs ranging from 12 to 120 ppm; these results show that cellulose is an effective scavenging agent for BCME.

Results. BCME in vapor form could originate in air from its precursors formaldehyde and chloride ions.

In closed systems, an occurrence of maximum values of BCME concentration was observed at certain temperatures.

When the BCME analyses were closely spaced while the temperature of the air was slowly varied, very rapid fluctuations in the BCME concentration were found.

The water content of the air seemed to have only a little effect on the formation and disappearance of BCME in air.

When the effect of the individual BCME precursors in excess was studied, it was found that (i) hydrogen chloride in excess tended to accelerate the disappearance of BCME in air, while (ii) formaldehyde in excess tended to protect BCME from disappearing.

As found by means of the gas chromatography-mass spectroscopy technique, the concentrations of BCME in the air that contained formaldehyde and chloride ions were confirmed to be built up in air, ie, in the gaseous phase. Only very low concentrations of BCME were formed when air containing a high concentration of formaldehyde and air containing a high concentration of chloride ions were simultaneously injected into the gas chromatography-mass spectroscopy setup.

It was found that the rate of disappearance of BCME in glass vessels depended upon the following factors: (i) the type of glass and its treatment, (ii) the volume of the vessel, and (iii) the input concentration of BCME in the vessel.

Discussion. The discovery of maximum values of BCME concentration when BCME is formed in air from formaldehyde and chloride ions might prove important from the point of view of occupational hygiene. It might be possible for BCME to be formed in air pockets with suitable concentrations of formaldehyde, chloride ions, and water vapor and with a suitable temperature. From these pockets, the ready-formed BCME,

which is relatively stable in air (even humid air), could then diffuse into other parts of the workplace atmosphere.

Laboratory simulation experiments performed with high concentrations of formaldehyde and chloride ions in air can scarcely give a satisfactory answer to the question of how much BCME is (or can be) formed in air at formaldehyde and chloride ion concentrations of 0.1 to 10 ppm, which are encountered in workplaces and sometimes also in the general atmosphere. The reasons are as follows: (i) the equilibrium constants K_1 (see table 8), calculated in the conventional way, spread too much (especially if experimental results by earlier researchers are taken as a basis) and (ii) if the constants K_1 are used for calculating those concentrations of BCME which might be expected to be formed from actually occurring concentrations of formaldehyde and chloride ions in the workroom air, then the results differ by many orders of magnitude from the concentrations of BCME which were actually determined in several workplaces.

The extreme sensitivity of BCME to impurities and the quality of the surfaces with which it comes in contact is a factor that makes the experiments and analyses difficult, sometimes even impossible.

The decomposition of BCME is catalyzed by hydrogen chloride. Thus the spontaneous disappearance of BCME can be supposed to be autocatalyzed by the hydrogen chloride released in the process.

It is difficult to give a suitable explanation for the variations of BCME concentration in air as a consequence of small changes of, above all, temperature. It is probable that some complex phenomena are involved, such as adsorption and/or decomposition on the reactor walls, the amount of formaldehyde available for the reaction, etc.

As regards formaldehyde in the system, it is consumed by two reactions: (i) a polymerization reaction catalyzed by chloride ions which is about four orders of magnitude more rapid than the formation of BCME and (ii) the actual reaction of BCME formation.

Future research will have to study the role of water vapor in the systems air/BCME/water vapor and air/BCME/formaldehyde/chloride ions/water vapor. The results so far obtained are sometimes contradictory. Higher water vapor content ought to accelerate the decomposition of BCME, but in some experiments it contributed to the sta-

Table 12. Occurrence of bis(chloromethyl)ether (BCME) in the headspace gases of reactors containing various concentrations of formaldehyde, zinc chloride, water, and methanol, with and without acidification with hydrochloric acid. Gas samples for analysis were taken directly out of the reactors. (The reactant concentrations are given in mole-percents).

System	Reactants	Reactor 1	Reactor 2	Reactor 3
Nonacidified, 20°C, samples taken from the 25th to the 62nd min	Formaldehyde	1.0	4.3	7.4
	Zinc chloride	8.7	7.5	6.4
	Water	90.1	87.0	84.2
	Methanol ^a	0.2	1.2	2.0
	Total	100.0	100.0	100.0
	BCME in ppm	None	None	None
Acidified, 20°C, three samples from each reactor within 60 min	Formaldehyde	0.8	3.6	6.4
	Zinc chloride	7.2	6.3	5.6
	Water	87.9	85.6	83.3
	Methanol ^a	0.2	1.0	1.7
	Hydrochloric acid	3.9	3.5	3.0
	Total	100.0	100.0	100.0
	BCME in ppm			
	Immediately	None	None	None
	After 3 d and heating to			
	24°C	None	None	None
	50°C	None	None	None
	100°C	0.02	None	None

^a The 35 % formaldehyde solution used contained about 10 % of methanol as a stabilizer.

bility of BCME in air instead. No explanation can be offered for this phenomenon.

The gas chromatography-mass spectroscopy technique is suitable for measuring concentrations of BCME in air in the presence of formaldehyde and chloride ions, as practically no BCME is additionally formed from its precursors on the gas chromatograph column filling.

Bis(chloromethyl)ether formation experiments in the liquid phase

The experiments with the liquid phase were made in two series: (i) in systems involving paraformaldehyde (or formaldehyde solution), zinc chloride, hydrochloric acid, and water and (ii) in solutions of a urea/formaldehyde resin containing free formaldehyde and chloride ions. The first series was designed to yield information about the possibilities of BCME formation as dependent on the acidity and water content of those reaction mixtures which might form BCME. The second series was the actual investigation of a formaldehyde-based resin system containing both BCME precursors.

The urea/formaldehyde resin was chosen to represent all three formaldehyde-based resins because it is the most common type of these resins.

Experimental procedure. There were usually four reactors with a volume of 1.4 l each on the water bath, and air samples were taken out of the reactors by means of a metering syringe with a hollow needle. The sample-taking was done either directly out of the reactor headspaces, through the septum in the respective reactor lid, or the reactors were flushed with a certain volume of artificial air (distributed by the rotameter system) and the BCME-containing air was collected in saran bags (usually of 10 l in volume), wherefrom gas samples were taken for analysis.

In these experiments, the reactants were brought together in liquid form, but the concentrations of BCME were measured in the headspace air, ie, in the gaseous phase. The BCME concentrations in the liquid reaction mixtures in the reactors were not investigated.

In systems involving formaldehyde, zinc

Table 13. Occurrence of bis(chloromethyl)ether (BCME) in the headspace gases of reactors containing various concentrations of paraformaldehyde, hydrochloric acid, zinc chloride, and water. The reactant concentrations are given in mole-percents. The reactor headspaces had volumes of about 1 l each. The BCME concentrations were determined in gases transferred to the saran bags.

Experimental conditions	Reactants	Reactor 1	Reactor 2	Reactor 3	Reactor 4
20°C, reaction time 60 min, reactor headspace volumes diluted with 7 l dry air each, transfer time 20 min	Hydrochloric acid	8.1	0.7	19.6	—
	Paraformaldehyde	5.3	0.5	12.9	11.1
	Zinc chloride	0.02	0.004	—	2.4
	Water	86.6	98.8	67.5	86.5
	Total	100.0	100.0	100.0	100.0
	BCME in ppm	0.01	0.01	360	0.03
25°C, reaction time 60 min, reactor headspace volumes diluted with 10 l of dry air each, transfer time 20 min	Hydrochloric acid	1.6	1.6		
	Paraformaldehyde	0.8	0.8		
	Zinc chloride	0.003	0.003	Not operated	
	Water	97.6	97.6		
	Total	100.0	100.0		
	BCME in ppm	0.01	0.01		
28°C, reaction time 60 min, reactor headspace volumes diluted with 10 l of dry air each, transfer time 20 min	Hydrochloric acid			3.3	3.3
	Paraformaldehyde			1.8	1.8
	Zinc chloride	Not operated		0.003	0.003
	Water			94.9	94.9
	Total			100.0	100.0
	BCME in ppm			0.01	0.01

chloride, and water, no BCME was found. After acidification with hydrochloric acid, no BCME was found in the analyses performed on the same day and only a small amount of BCME (0.02 ppm) was found in one of the acidified systems after 3 d of standing and after being heated up to 100°C.

The respective system in reactor 1 (see table 12) was characterized by the highest concentration of hydrochloric acid and zinc chloride. It also had the lowest concentration of formaldehyde. This occurrence shows that the acidity of the system was decisive.

Systems involving paraformaldehyde (the mole-percent concentrations of which are given in formaldehyde equivalents), zinc chloride, water, and hydrochloric acid showed that a high concentration of hydrochloric acid (ie, a very low pH value) was needed for an appreciable concentration of BCME to be obtained in air.

While hydrogen chloride concentrations of 1.6 to 8.1 mol-% achieved only 0.01 ppm of BCME in air, a concentration of 19.6 mol-% of hydrogen chloride made the BCME concentration in air increase to 360 ppm (table 13).

Thus only systems with very low contents of water and/or very low pH values can form appreciable concentrations of BCME in air.

In experiments involving solutions of urea/formaldehyde resins that were performed in 1.4-l reactors with headspace volumes of about 1 l, the resins used were both original and enriched with free formaldehyde. As chloride ion donors, zinc chloride, magnesium chloride hexahydrate, ammonium chloride, and sodium chloride were used.

Table 14 shows the respective results. The BCME formation in the headspace air was very low, from 0.005 to 0.03 ppm. The fact that the value of 0.20 ppm occurred only once is difficult to explain. As it seemed improbable, in the first place, the analyses were repeated, but the results did not change. The whole experiment was, however, not repeated, and, therefore, this value cannot be considered confirmed.

Characteristically, the highest BCME concentrations were achieved after rather long reaction times and at temperatures of about 40°C.

Further investigations concerned the effect of the geometry and kinematics of stirring, the effect of the catalysts, and the decomposition of BCME in atmospheres containing formaldehyde, hydrogen chloride, and water vapor.

As regards the effect of the geometry and kinematics of stirring, an alkylating mixture

Table 14. Formation of bis(chloromethyl)ether (BCME) from a urea/formaldehyde resin solution and chloride catalysts.

Reaction time (min)	Temperature (°C)	Resin solution (g)	Formaldehyde solution ^a (g)	Zinc chloride (g)	Magnesium chloride ^b (g)	Ammonium chloride (g)	Sodium chloride (g)	BCME concentration ^c (ppm)
51-118	20-32	420	—	40	—	—	—	0.01
57	20	420	—	—	40	—	—	0.01
100	27	420	—	—	40	—	—	0.02
124	34	420	—	—	40	—	—	0.01
63	20	420	—	—	—	40	—	0.00
106-130	28-36	420	—	—	—	40	—	0.01
69	20	420	—	—	—	—	40	0.02
112-136	29-38	420	—	—	—	—	40	0.01
109	21	420	2.2	40	—	—	—	0.01
174	34	420	2.2	40	—	—	—	0.00
198	41	420	2.2	40	—	—	—	0.20 (!)
222	43	420	2.2	40	—	—	—	0.01
228	42	420	2.2	40	—	—	—	0.02
115-180	23-36	420	2.2	—	40	—	—	0.01
204	42	420	2.2	—	40	—	—	0.03
121	22	420	2.2	—	—	40	—	0.01
186-210	37-41	420	2.2	—	—	40	—	0.02
240	43	420	2.2	—	—	40	—	0.01
127-192	25-38	420	2.2	—	—	—	40	0.01
216	42	420	2.2	—	—	—	40	0.03
246	43	420	2.2	—	—	—	40	0.01
44-426	16-42	420	—	40	—	—	—	0.000-0.005
50-432	17-41	420	2.2	40	—	—	—	0.000-0.005
56-460	18-42	420	4.3	40	—	—	—	0.000-0.005
62-466	19-41	420	6.5	40	—	—	—	0.000-0.010

^a The formaldehyde solution was 35 %, containing about 10 % of methanol as a stabilizer.

^b The magnesium chloride used was the hexahydrate $\text{MgCl}_2 \cdot 6\text{H}_2\text{O}$.

^c The BCME concentrations were determined in the headspace gases.

was used which was either stirred or not stirred and in which the air stream was introduced either underneath or above the liquid reaction mixture. Table 15 shows the results. The same BCME concentrations were obtained when the air stream was introduced under the surface of the reaction mixtures, regardless of whether the respective mixture was stirred or not. When the reactor was not stirred and the air was introduced above the reaction mixture, the BCME concentration in the headspace air dropped to about 25 % of that of the remaining three arrangements.

In experiments with alkylating mixtures with and without a chloride catalyst, it was shown that a small amount of zinc chloride in the reaction mixture increased the concentration of BCME in the headspace air by about 25 % at 20°C.

The saran bags filled with air containing BCME, hydrogen chloride, formaldehyde, and water vapor from the respective experiments were used to study the spontaneous disappearance of BCME at 20°C. It was

shown that this disappearance could be expressed by an exponential equation having the form of

$$c_t = c_0 \times e^{a \cdot t} \quad (\text{eq 7})$$

where c_t = concentration of BCME in parts per million at time t , c_0 = initial concentration of BCME in parts per million at time $t=0$, t = time in hours, and a = constant of decomposition.

The actual equation as calculated from the results was

$$c_t = 430 \times e^{-(0.0094 \pm 0.0022) \cdot t} \text{ (ppm)} \quad (\text{eq 8})$$

The reaction half-time was 60 to 96 h (average value 70 h). In addition, several liquid phase experiments were performed with the use of the microreactor technique. Table 16 shows the results of experiments involving the systems hydrochloric acid/paraformaldehyde/water/chloride catalyst. The concentrations of BCME in the headspace air were greatly dependent on the strength of the hydrochloric acid in the systems.

Table 15. Effects of the geometry and kinematics of stirring upon the occurrence of bis(chloromethyl)ether (BCME) in the headspaces of alkylating mixtures.

Experimental conditions in the reactors	Stirring	Air introduction with respect to the reaction mixture surface	BCME concentration as determined in the saran bag gases (ppm)	
			Mean	SD
Reaction mixture components in mole-%: Hydrochloric acid 20.00, paraformaldehyde 10.95, zinc chloride 0.05, water 69.00, 20°C, reaction time 60 min, contents of each reactor diluted with 7.5 l of dry air	Yes	Underneath	450	45
	Yes	Above	460	27
	No	Underneath	450	13
	No	Above	90	5
Average value for reactors 1–3			453	16

With 37 % hydrochloric acid, the BCME concentration in the headspaces of the microreactors was of the 10^2 to 10^4 ppm order of magnitude. The BCME concentrations dropped steeply with the decreasing concentrations of hydrochloric acid. The coefficients of correlation show that the exponential fit of the type

$$c_{\text{BCME}}(\text{ppm}) = a \times e^{b \cdot c_{\text{HCl}}(\%)}$$
 (eq 9)

is best. A similar picture was obtained when the system sulfuric acid/zinc chloride/para-

Table 16. Concentrations of bis(chloromethyl)ether (BCME) as dependent on the concentration of hydrochloric acid (HCl), type of chloride catalyst, and temperature^a. In the equation $c_{\text{BCME}}(\text{ppm}) = a \times e^{b \cdot c_{\text{HCl}}(\%)}$, a and b are constants and r^2 is the coefficient of determination.

Temperature (°C)	Catalyst	a	b	r^2
25	Zinc chloride	4.04×10^{-8}	0.6562	0.98
	Magnesium chloride	3.38×10^{-8}	0.6641	0.99
50	None	5.40×10^{-16}	1.1743	0.99
	Zinc chloride	1.78×10^{-16}	1.2065	0.99
75	Magnesium chloride	1.37×10^{-14}	1.0886	0.97
	None	1.55×10^{-11}	0.9621	0.88
90	Zinc chloride	3.31×10^{-10}	0.8577	0.93
	Magnesium chloride	2.12×10^{-13}	1.1035	0.98
90	None	7.19×10^{-16}	1.0925	0.97
	Zinc chloride	8.80×10^{-16}	1.0873	0.93
90	Magnesium chloride	7.95×10^{-17}	1.1642	0.99
	chloride			

^a The experiments were performed in closed 25-ml microreactors containing 0.1 g of paraformaldehyde, 1.0 ml of HCl in the respective concentration, and 0.05 ml of the saturated chloride catalyst solution each.

formaldehyde/water was used (table 17). On the other hand, when systems involving 100 mg of paraformaldehyde, 225 mg of zinc chloride, and 2 ml of formic, acetic, or phosphoric acid in various concentrations and at various temperatures were used, the result was that phosphoric acid gave measurable BCME concentrations in the headspace gases of the microreactors at all temperatures (25, 50, and 100°C) and in acid concentrations from 85.0 to 76.5 %, while formic acid yielded measurable BCME concentrations practically only at 100°C with acid concentrations ranging from 99.0 to 89.1 %, and acetic acid led to measurable BCME concentrations only at 100°C, with the highest acid concentration available of 96.0 %.

The most commonly used buffer systems (Merck-Puffer-Titrisol) were also tested. No

Table 17. Formation of bis(chloromethyl)ether (BCME) in the sulfuric acid/zinc chloride/formaldehyde/water system. Each microreactor contained 100 mg of paraformaldehyde, 225 mg of zinc chloride, and 2.0 ml of sulfuric acid in the respective concentration. The reaction temperature was 25°C.

Concentration of sulfuric acid (%)	Evolved amount of BCME (ppm)	Reaction time (min)
96.0	400	46
86.4	> 1,200	54
76.8	> 1,200	68
67.2	> 1,200	75
57.6	250	290
48.0	0.7	278
38.4	0.005	265
28.8 (ca 3 N)	0	256
19.2	0	346
9.6	0	122
0	0	109

BCME formation was observed at 25, 50, and 75°C with buffer solutions having pH values of 1 and 2 that were based on hydrochloric acid and glycine and hydrochloric acid and citrate, respectively. Two milliliters of these buffer solutions were used together with 100 mg of paraformaldehyde and 225 mg of zinc chloride. The question was whether the organic compounds contained in the buffers acted as inhibitors or scavengers.

The effect of accompanying matter on the residual concentration of BCME in specially treated and untreated microreactors was tested as well.

The microreactors filled with ambient air were injected with 2.4 ppm of BCME and left standing in darkness for 21 h.

The average results (of two to four microreactors each) showed, eg, that the specially treated microreactor vials without additions retained about 7 % of the originally injected amount of BCME, while the BCME residues in untreated vessels were three times as high (21 %). Microreactors containing 1 g of untreated glass fiber exhibited a BCME residue of 8.8 %, while microreactors containing specially treated glass fiber had no BCME left over. As regards the quartz fiber (1 g in each microreactor), the residues were 2.8 % with untreated and 1.9 % with specially treated fiber.

Additions like wood chips and Merck molecular sieve 3 Å (1 g), filter paper (36 cm²=270 mg), as well as distilled water, 96 % sulfuric acid, 37 % hydrochloric acid, and concentrated acetic and formic acid (1 ml each) had a totally decomposing effect on the BCME contained in the microreactor headspace air, no analyzable traces being left after 21 h. All experiments were performed at 20°C.

Results. The nonacidified systems formaldehyde/zinc chloride/water were not found to lead to an occurrence of gaseous BCME in reactor headspaces.

The systems formaldehyde/hydrogen chloride/zinc chloride/water were capable of making gaseous BCME appear in reactor headspaces in appreciable concentrations only if the concentration of hydrochloric acid was very high.

The concentration gradient of hydrochloric acid was very steep. With about 10 mol-% of hydrogen chloride the resultant BCME concentrations in the reactor

headspace was in the 0.01 ppm order of magnitude, with about 20 mol-% as high as in the 10² to 10³ ppm order of magnitude. A doubling of the hydrogen chloride concentration in this range entailed thus an increase of the gaseous BCME concentration in the headspace by a factor of 10⁴ to 10⁵.

The development of BCME in solutions of a urea/formaldehyde resin which contained both free formaldehyde and chloride ion donors (various chlorides) was very low when the reaction mixtures were heated slowly. The respective concentrations in the gas phase of the headspaces varied from about 0.005 to about 0.03 ppm.

When chloroalkylating mixtures containing the system formaldehyde/hydrochloric acid/zinc chloride/water were stirred (either mechanically or by introduction of a carrier gas under the surface of the reaction mixture), the concentrations of BCME in the reactor headspaces were of the 10² to 10³ ppm order of magnitude. When the same reaction mixture was not stirred, the concentration of BCME in the headspace air decreased to about one-quarter of the presented figures.

Chloroalkylating mixtures containing zinc chloride as the catalyst produced about 25 % more BCME than the same mixtures without the chloride catalyst.

When saran sacks were filled with gaseous mixtures of air/BCME/water vapor/formaldehyde/hydrogen chloride that contained 10² to 10³ ppm of BCME and the disappearance of BCME was investigated as a function of time, it was found that the respective equation was of exponential character and that the half-time of BCME disappearance was from 60 to 96 h at 20°C.

The question arises, however, of what happened to BCME in the saran sacks. Besides decomposition, there is also the possibility that some BCME was absorbed by the material of the saran sacks as it is probably a solvent or at least a swelling agent for this type of polymer (a copolymer of vinylidene chloride with vinyl chloride and/or vinyl acetate).

Organic acids (such as formic and acetic acid) were found capable of leading to measurable BCME concentrations in the headspace gases only if they were used (in connection with paraformaldehyde and zinc chloride) in the highest concentrations and at elevated temperatures. Phosphoric acid led

to measurable BCME concentrations also at room temperature and in greater dilutions than the mentioned organic acids.

Systems involving sulfuric acid, formaldehyde, zinc chloride, and water were also found to be strongly dependent on the concentration of the acid. While the highest concentrations of sulfuric acid produced gaseous BCME concentrations in the headspace gases in the 10^3 to 10^4 ppm order of magnitude, the concentration of about 29 % (about 3 N sulfuric acid) produced no measurable concentrations of BCME.

Certain materials (both organic and inorganic) possess the property of acting as BCME scavengers in BCME-containing atmospheres. Of particular importance are cellulose-containing materials which scavenge both formaldehyde and BCME (both compounds happen to act as cellulose cross-linkers).

Discussion. The occurrence of BCME above liquid systems involving formaldehyde, hydrochloric acid, and, possibly also, a metal chloride is strongly dependent upon the concentration of hydrochloric acid, ie, upon the pH value.

There is an exponential relation between the concentration of BCME in parts per million in the headspace gases and the concentration of hydrochloric acid in the liquid phase.

Thus in order to achieve measurable occurrences of BCME in the gas phase above the liquid reaction mixtures containing formaldehyde and chloride ions, very high concentrations of strong acids are needed and/or the amount of water in the system must be reduced to a minimum. Inorganic acids are much more effective than organic ones.

Even if some BCME was found in the gas phase above stirred solutions of formaldehyde-based resins that contained both free formaldehyde and chloride ions and that were slowly heated, there need not be any health risk, as closed blending vessels can be used and the BCME developed in the headspaces can be liquidated, eg, by injections of steam or ammonia before the vessels are opened, in industrial operations.

Actually, the respective experiments represented the worst imaginable case, with the resin solutions containing great amounts of free formaldehyde and chloride ions. Besides, these solutions were stirred a relatively

long time and heated. Such situations do not usually occur in industry.

It is of great advantage if resin solutions containing BCME precursors are processed in conjunction with materials that are BCME scavengers. One of the best scavenging materials is cellulose (contained, eg, in paper or in cellulosic fibers). It can contribute a great deal to the liquidation of BCME in case the latter is formed in the process in question.

The investigations performed concerned situations in which BCME was measured above liquid mixtures containing acids, chloride ions, formaldehyde, and water. No measurements were made regarding the possible concentrations of BCME in the liquid phase itself.

So far, a general consensus of opinion has been that a release of BCME from the liquid into the gaseous phase is scarcely possible. Radding et al (231) wrote as follows:

BCME is extremely unstable in water. It decomposes with a half-life of 10–40 seconds. Fortunately, it fails to move from water to air in measurable amounts prior to decomposition, even within small reaction vessels [p 27].

This situation might, however, apply only to systems that contain a relatively large percentage of water. But the question is whether it also applies to systems with very low pH values which contain only very little water. If BCME does not decompose in them, it might even be able to evaporate from them.

Theoretically, there are three possibilities of BCME formation from its precursors if a two-phase system is considered which is composed of a liquid-phase mixture containing the BCME precursors and a gas phase above it:

- a BCME is formed in the liquid phase and evaporates from it into the gas phase;
- b BCME is formed at the interface of both phases, the actual BCME formation occurring in the gas phase, in a very thin gas layer in which the concentration of formaldehyde and chloride ions is very high before being diluted through the upward passage;
- c BCME is formed in the gas phase, a relatively long way from the liquid phase.

Theoretically it could really be expected that point a would be of great importance as the formation of BCME from its precursors is an ionic process. On the other hand, the

Table 18. Experimental design for the complex investigation of predried resin solutions under conditions simulating the drying and curing process – Description of the complete program.

Step	Operating instructions
1	Inject 1 ml of a resin solution (without or with additional formaldehyde solution, without or with catalyst) into each microreactor intended to contain a resin sample for testing Predry the microreactors at 40°C in order to evaporate the greatest part of the solution water and to obtain solid resin films on the inner walls of the microreactors Use new vials, rinse them with 100% methanol and dry them at 105°C Cover the microreactors containing the dried resin films with Teflon caps and close them hermetically
2	Place the microreactors in their respective holders onto the oil bath Where needed, insert two hollow syringe needles by sticking them through the caps in order to make the inner space of the microreactors communicate with the outer atmosphere so that the water vapor that evolves from the resin films during the heating can escape
3	Set the temperature controller to the drying temperature (eg, 120°C) and start the heating
4	When the drying temperature is reached, flush the following microreactors with dry air (through one needle in, through the other out) and then pull the hollow needles out of the following microreactors: 3–13–23–33, 4–14–24–34, 7–17–27–37, and 9–19–29–39
5	Inject 1 μ l of BCME 10^{-4} into the following microreactors: 7–17–27–37 and 9–19–29–39
6	Analyze the gases from the following microreactors for BCME content (drying temperature): 1–11–21–31, 3–13–23–33, 4–14–24–34, 7–17–27–37, and 9–19–29–39;
7	Set the temperature controller to the curing temperature (eg, 180°C) and start the heating
8	When the curing temperature is reached, flush the following microreactors with dry air (similarly as in point 4) and pull the hollow needles out of the following microreactors: 5–15–25–35, 6–16–26–36, 8–18–28–38, and 10–20–30–40
9	Inject 1 μ l of BCME 10^{-4} into the following microreactors: 8–18–28–38 and 10–20–30–40
10	Analyze the gases from the following microreactors for BCME content (curing temperature): 2–12–22–32, 5–15–25–35, 6–16–26–36, 8–18–28–38, and 10–20–30–40
11	Stop the experiment, cool the oil bath and liquify the residual BCME in those microreactors where it was found. Discard the microreactors

half-time of BCME hydrolysis in aqueous media is very short (less than 40 s at 20°C and neutral pH). Thus it might be argued that point a would apply only for very strongly acidic media with suppressed hydrolysis of BCME because only under these circumstances can BCME be volatilized.

These conditions will have to be investigated in further BCME research because they are of great importance for those industries in which BCME formation can occur.

Bis(chloromethyl)ether formation experiments in the solid phase

The microreactor method operating with 25-ml potassium glass vials increased the operational safety of the experiments and enhanced the productivity of experimentation.

Only small amounts of reagents (of the order of magnitude of 10 to 1,000 mg) are needed in this method, but measurable amounts of BCME can be formed in the microreactors and analyzed by gas chromatography-mass spectroscopy under suitable conditions.

graphy-mass spectroscopy under suitable conditions.

One bath with 40 positions allows as many separate experiments to be run.

The most efficient experimental designs operate with both baths at the same time (water bath for temperatures of up to 100°C and oil bath for temperatures of up to 200°C).

Experimental procedure. On the whole, 24 resin solutions were tested. These comprised three types of resins, two different contents of free formaldehyde, and four different types of chloride catalysts. The three types of resin were the following: (i) phenol/formaldehyde resin solutions, (ii) urea/formaldehyde resin solutions, and (iii) melamine/formaldehyde resin solutions. The two different contents of free formaldehyde were as follows: (i) the natural free formaldehyde content of the resins, and (ii) an increased content of free formaldehyde from the addition of 3 g of 35 % formaldehyde solution to 100 g of each respective resin solution. The

Table 19. Experimental design for the complex investigation of predried resin solutions under conditions simulating the drying and curing process – Description of the abbreviated program^a. [Catalysts: A = none (microreactors 1–10), B=magnesium chloride (microreactors 11–20), C=zinc chloride (microreactors 21–30), D=ammonium chloride (microreactors 31–40)].

Step	Operating instructions
1	Proceed as stated in the complete program
2	Proceed as stated in the complete program
3	Proceed as stated in the complete program
4	Proceed as stated in the complete program
5	Proceed as stated in the complete program
6	Carry out the analyses as follows: analyze microreactors 11 and 21; if no BCME is found, do not analyze microreactors 1 and 31; analyze microreactors 13 and 23; if no BCME is found, do not analyze microreactors 3 and 33 as well as 4–14–24–34; analyze microreactors 7–17–27–37 and 9–19–29–39
7	Proceed as stated in the complete program
8	Proceed as stated in the complete program
9	Proceed as stated in the complete program
10	Carry out the analyses as follows: analyze microreactors 12 and 22; if no BCME is found, do not analyze microreactors 2 and 32; analyze microreactors 15 and 25; if no BCME is found, do not analyze microreactors 5 and 35 as well as 6–16–26–36; analyze microreactors 8–18–28–38 and 10–20–30–40
11	Proceed as stated in the complete program

^a The abbreviated program omits 16 of 40 microreactors and is thus 40 % shorter. It is based on the following considerations:

- If no BCME is detected in microreactors 11 and 21 (where the catalysts are magnesium chloride and zinc chloride, respectively), then it is practically out of the question that BCME might be formed in microreactors 1 and 31, which contain, respectively, no catalysts and ammonium chloride.
- The same argument as in consideration a applies to microreactors 13 and 23 (compared with 3 and 33), to 12 and 22 (compared with 2 and 32), and to 15 and 25 (compared with 5 and 35).
- The series 4–14–24–34 and 6–16–26–36 are back-ups for the series 3–13–23–33 and 5–15–25–35, respectively. The back-up series are there only in case that BCME is discovered in the series 3–13–23–33 and/or 5–15–25–35 in order to broaden the experimental base.

four different types of chloride catalysts were: (i) no catalyst at all (marked A), (ii) 5 g of magnesium chloride hexahydrate added to 100 g of resin solution (marked B), (iii) 5 g of zinc chloride added to 100 g of resin solution (marked C), and (iv) 5 g of ammonium chloride added to 100 g of resin solution (marked D).

Preliminary experiments were run in order to determine the best way of introducing the resin solutions into the microreactors.

The use of resin carriers, such as small wads of glass wool, small wads of quartz wool, and small squares of filter paper, was rejected after it had been found that these carriers are BCME scavengers. For this reason the resin samples were inserted into the microreactors without any carriers or supports.

Two different types of caps were tested as well, namely, ordinary rubber caps and Teflon-lined caps. In preliminary experiments it was found that Teflon-capped microreactors

injected with pure BCME conserved a much greater amount of BCME than rubber-capped microreactors, regardless of reaction time and reaction temperature. Thus it was concluded that rubber caps contributed to uncontrolled losses of BCME inside the microreactors.

In order to reduce a possible surface effect of the inside glass walls of the microreactors, care was taken to cover these walls with a predried resin film during the preparation of the microreactors for the experiments.

The following requirements were formulated a priori for the development of the testing system:

a testing of the resins without ventilation while the water vapor evolved in drying remained inside the reactors;

b testing of the resins without ventilation while the water vapor evolved in curing remained inside the reactors;

RESIN SOLUTION WITHOUT CATALYST (A)	RESIN SOLUTION WITH CATALYST (B)	RESIN SOLUTION WITH CATALYST (C)	RESIN SOLUTION WITH CATALYST (D)	
1	11	21	31	REACTORS WITH PREDRIED RESIN. WITHOUT HOLLOW NEEDLES
2	12	22	32	REACTORS WITH PREDRIED RESIN. WITHOUT HOLLOW NEEDLES
3	13	23	33	REACTORS WITH PREDRIED RESIN. WITH TWO HOLLOW NEEDLES
4	14	24	34	REACTORS WITH PREDRIED RESIN. WITH TWO HOLLOW NEEDLES
5	15	25	35	REACTORS WITH PREDRIED RESIN. WITH TWO HOLLOW NEEDLES
6	16	26	36	REACTORS WITH PREDRIED RESIN. WITH TWO HOLLOW NEEDLES
7	17	27	37	REACTORS WITH PREDRIED RESIN. WITH TWO HOLLOW NEEDLES
8	18	28	38	REACTORS WITH PREDRIED RESIN. WITH TWO HOLLOW NEEDLES
9	19	29	39	EMPTY REACTORS WITH TWO HOLLOW NEEDLES
10	20	30	40	EMPTY REACTORS WITH TWO HOLLOW NEEDLES

Fig 17. Arrangement of the microreactors for the complex investigation of predried resin solutions under conditions simulating the drying and curing process.

c testing of the resins under drying conditions after ventilation of the water vapor evolved from the resins in the time from the start of the experiments until the respective drying temperature was reached;

d testing of the resins under curing conditions after ventilation of the water vapor evolved from the resins in the time from the start of the experiments until the respective curing temperature was reached;

e spiking with BCME at the drying temperature and, at the same time, performing of a control experiment with BCME in an empty air-filled reactor under the same conditions;

f spiking with BCME at the curing temperature and, at the same time, performing of a control experiment with BCME in an empty air-filled reactor under the same conditions.

The drying temperature was standardized at 120°C, and the curing (hardening) temperature at 180°C.

After several variants were tried, the experimental design was standardized according to tables 18 and 19 and fig 17.

Two programs can be used for the execution of the test, namely, either a full program (table 18) or an abbreviated program (table 19). The microreactor arrangement for the full program is presented in fig 17.

The abbreviated program omits 16 out of 40 microreactors and is thus 40 % shorter.

The experiments for each type of resin solution were run four times in the standardized version of the full program (twice with the original and twice with the increased contents of free formaldehyde) and twice in the standardized version of the abbreviated program (once with the original and once with the increased contents of formaldehyde).

The results of all the experiments, without exception, were negative, ie, no BCME was discovered in any of the microreactors, both for resins with the original contents of free formaldehyde and for those with the increased contents of it. The experiments turned out to be negative regardless of whether or not a catalyst was used and regardless of the type of the chloride catalyst used.

In the preparation of the resins for the experiments, the necessary amount of the resin solution (1 g) was introduced into each microreactor and the open microreactors were then subjected to a temperature of about 40°C under continuous rolling for about 48 h in order to evaporate as much water as possible before the start of the actual experiment. The results were thin resin films on the inside glass walls of the microreactors.

Of particular interest were the results of the spiking experiments.

For spiking, 1.2 ppm of BCME vapor was injected into the microreactors. Both the microreactors with resins and the empty air-filled microreactors received this treatment. The aim was to determine whether the gases released in the drying and curing of the resins were "BCME-friendly." The results showed that these gases were not "BCME-friendly," because BCME residues always turned out to be lower in the microreactors with resins than in those without them.

This finding led to the conclusion that either the resins themselves or the gases

Table 20. Experimental design for investigating the effect of pyrolysis gases on the concentration of bis(chloromethyl)ether in dry air – Description of the program.

Step	Operating instructions ^a
1	Put all C microreactors (ie, C1 through C3, C11 through C13, C21 through C23, and C31 through C33) into the water bath; put microreactors W3 through W5, W13 through W15, and W23 through W25 into the oil bath
2	Analyze controls 1 through 3 (ie, microreactors W23 through W25, C21 through C23, and C31 through C33) at room temperature
3	Increase the temperature of the oil bath to the drying temperature (eg, 120°C)
4	After the drying temperature has been reached, put the microreactors with pyrolysis material (ie, W1–2, W11–12, and W21–22) into the oil bath
5	Run the oil bath 30 min at the drying temperature
6	Inject 0.5 ml of pyrolysis gases from microreactor W1 into each microreactor C1 through C3 and from microreactor W2 into each microreactor W3 through W5
7	Run the oil bath 30 min at the drying temperature
8	Analyze microreactors W3 through W5 and controls 1 through 3 (ie, microreactors W23 through W25, C21 through C23, and C31 through C33)
9	Increase the temperature of the oil bath to the curing temperature (eg, 180°C); while the temperature rises, analyze microreactors C1 through C3
10	Run the oil bath 30 min at the curing temperature
11	Inject 0.5 ml of pyrolysis gases from microreactor W11 into each microreactor C11 through C13 and from microreactor W12 into each microreactor W13 through W15
12	Run the oil bath 30 min at the curing temperature
13	Analyze microreactors W13 through W15 and microreactors C11 through C13
14	Analyze controls 1 through 3 (ie, microreactors W23 through W25, C21 through C23, and C31 through C33)
15	The experiment is finished; turn off the water bath and the oil bath and liquidate the BCME residues in the cold and cooled-off microreactors by injecting 1 ml of 25 % ammonia solution into each micro-reactor

^a During the whole experiment the water bath with microreactors C (cold) remains at 25°C and is agitated; the oil bath with microreactors W (warm) operates in the usual way.

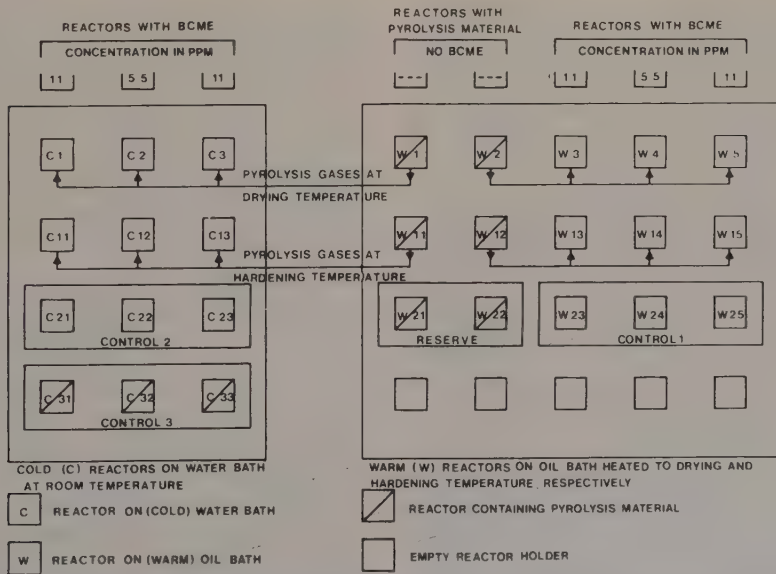


Fig 18. Microreactor arrangement on the water bath and on the oil bath for investigating the effect of pyrolysis gases on the concentration of bis(chloromethyl)ether (BCME) in air.

evolved from them in the enclosed microreactors at the temperatures of 120° or 180°C are capable of decomposing BCME under these conditions.

The gases emitted by the resins being dried and cured are composed mainly of water vapor and of pyrolysis (thermolysis) gases. Thus it became necessary to investigate which component of these gases decomposed BCME or contributed the most to its disappearance.

The following two experimental series were run in order to determine the effects of pyrolysis gases on BCME:

a In the first experiment pulverized chipboard bound with urea/formaldehyde resin and fireproofed with magnesium chloride was used. The outer surface of a sample of this chipboard containing 13 weight-% of magnesium chloride hexahydrate, 10 weight-% of urea/formaldehyde resin (dry substance), and 77 weight-% of wood chips (dry substance) was abraded on a milling machine, and 100 to 500 mg of these shavings were heated in closed microreactors to temperatures of 50, 100, 120, 150, and 180°C. Theoretically, BCME could be supposed to be formed by the heating of such chipboards, but no BCME was found in gas chromatographic-mass spectroscopic analyses of the gases released by these chipboard shavings in the respective experiments.

b In the second experiment a special procedure was developed for investigating the effect of pyrolysis gases on BCME. This procedure involved the use of both the water bath (as "cold bath") and the oil bath (as "warm bath"). The experimental design is shown in table 20 and fig 18.

These experiments, repeated three times for each pyrolysis material, showed that pyrolysis gases from filter paper (ie, practically pure cellulose) and from wood chips had no appreciable effect on the decomposition of BCME because BCME residues in microreactors with injections of pyrolysis gases were practically the same as BCME residues in those microreactors to which no pyrolysis gases were added.

When BCME was injected into cold microreactors with filter paper or with wood chips, it tended to disappear wholly after 6 h, in most experiments. This finding confirms the BCME-decomposing effect which was observed before (125).

In the aforementioned experiments, 25 mg of wood chips and 70 mg of filter paper were used. The injections were done with 0.5 ml of pyrolysis gases.

In order to eliminate the effect of water vapor, an additional experiment was made, at 180°C, in which the microreactors for producing pyrolysis gases, with 250 mg of wood chips or 270 mg of filter paper, contained also 1 g of molecular sieve 3 Å or 1 g of phosphorus pentoxide.

Even these dehydrated pyrolysis gases had no appreciable accelerating effect on the decomposition of BCME as compared with the microreactors that contained only BCME in air.

Results. The microreactor experiments simulating the actual processes of drying and curing formaldehyde-based resins showed that no BCME is formed in these processes from resins containing both free formaldehyde and chloride ions that originate from different chlorides.

The drying and curing resins, or the gases which they emit, were found to be BCME-unfriendly because they tended to eliminate the spiked BCME.

The gases emitted by the resins in the drying and curing processes are composed of pyrolysis (thermolysis) gases of unknown composition and of water vapor.

In the investigation of the pyrolysis gases, it was found that they did not affect the BCME concentration in air. Therefore it was concluded that water vapor was the factor responsible for BCME mopping-up in air.

As water vapor in the gaseous state does not decompose BCME, or does it only slowly, it was concluded that the active factor in BCME decomposition was liquid water with a very large surface, ie, tiny water droplets that are formed when water vapor condenses to visible fog.

In order to prove this hypothesis, a fourth experimental stage was planned and executed (see the section Destruction Experiments in the Gaseous Phase).

Discussion. The microreactor method is an original method developed for investigating the possible formation of BCME when formaldehyde-based resins are dried and cured.

It has several advantages, namely, (i) if BCME is formed, it is enclosed in capped microreactors from which it can be taken only by means of a hollow syringe needle for

injection into the gas chromatography-mass spectroscopy setup; (ii) only very small quantities of reactants can be used, and, in spite of this, analyzable amounts of BCME can be generated if the reaction conditions are favorable; (iii) a dangerous leakage of BCME is practically impossible, even high concentrations of BCME can be easily killed by an injection of a strongly alkaline solution into the microreactors, and an exploding microreactor delivers its contents to a liquid that renders the BCME innocuous; (iv) the large number of work positions in the liquid baths enhances the productivity of experimenting and allows the execution of complex experimental programs; and (v) the experimental arrangement is simple and easily serviceable and it is suitable also for experimenting with other dangerous compounds.

Although no BCME formation at all was observed in the simulation experiments involving resins that contained both formaldehyde and chloride ions, the use of chlorides, or chemicals which form or release chloride ions, is strongly advised against with such resins because BCME can be formed from formaldehyde and chloride ions once they have become integrated with the workroom atmosphere. A "background formation" of BCME in an atmospheric reaction, from formaldehyde and chloride ions, is entirely possible and imaginable. Actually, it was detected several times in earlier investigations.

Thus, while manufacturing operations that involve a drying and/or curing process for formaldehyde-based resins which contain chloride ions do not seem to lead to the formation of BCME during the actual processes, the situation is such that both formaldehyde and chloride ions, which have been released by these processes, can escape into the workroom air where BCME can be formed like in any other gaseous milieu that contains these two BCME precursors if the conditions are favorable.

Owing to the danger of an atmospheric reaction between formaldehyde and chloride ions, it is strongly recommended to keep formaldehyde as well as chemicals which form or release formaldehyde, strictly separated from hydrochloric acid and chlorides, as well as compounds which form or release chloride ions, especially if the pH value is low, and not to allow a mixing together of formaldehyde and chloride ions in air. These

chemicals ought to be stored in separate rooms.

Chemical reactions that necessarily involve both formaldehyde and chloride ions, in the gaseous, liquid, or solid phase, especially if low pH values are needed at the same time, must be performed in carefully monitored closed systems. BCME residues in the gaseous, liquid, or solid phase must be liquidated before the opening and emptying of the reaction vessels.

Bis(chloromethyl)ether destruction experiments in the gaseous phase

The decomposition of BCME by condensing water vapor, discovered during the previously described experiments, was studied in greater detail because it was thought that this phenomenon was of practical importance and that operational methods based on this principle could be used in industry to annihilate those amounts of BCME that happen to be formed in the reactors and/or escape into the workroom air.

Generally speaking, there are two mechanisms of BCME destruction, namely, solvolysis and radical oxidation.

Radding et al (231) pointed out that, in liquidating BCME, solvolysis would by far outweigh radical oxidation as the half-time of BCME decomposition in water is only 10 to 40 s.

Experimental procedure. The 1.4-l reactor used for BCME destruction experiments could be heated by means of an electric resistance heating nest that could be hoisted and lowered on a movable platform and be brought into contact with the lower hemispherical part of the glass reactor.

The same platform could also carry a large beaker with cold water into which the reactor could be immersed for cooling purposes.

For use with this reactor a small brass retort that contained several milliliters of water was made. The retort had a wooden handle on a metallic stick, and its neck was drawn out about 10 cm. There was a hollow needle mounted at the end of the neck, and this needle could be stuck through the septum in the reactor lid. In operation, the retort was filled with water and then heated in a Bunsen flame until it started to deliver a thin stream of steam under pressure. Then the neck was heated by the flame and the steam became

superheated. With the help of this retort superheated steam could be injected into the reactor.

In principle, the reactor could be operated in two ways: (i) by making the water vapor contained in the air inside the reactor condense as a consequence of decreasing the temperature of the air to less than the dew point, and (ii) by injecting saturated or superheated steam into the air in the reactor.

In both instances, small droplets of liquid air were formed and these quickly destroyed the BCME present in the air by first adsorbing it on the surface and then decomposing it, according to the formula:



The formaldehyde and hydrochloric acid that originate in the presented reaction are immediately dissolved in the water of the droplets. As the concentrations of formaldehyde and hydrochloric acid solutions that are formed in this way are very low, there is no possibility of BCME being reformed in any significant amount in this liquid phase.

Before the actual testing of the scavenging effect of condensing water vapor, several experiments were made with BCME in air-filled reactors. In a reactor with falling air temperature, the BCME content, which had been dropping, temporarily stabilized at about 35 % of the original input value when a temperature of about 65°C was reached. In a reactor with rising air temperature, a temporary stabilization of the BCME residual content could be achieved in dry air provided no hot spots in the reactor wall originated. Such an occurrence can rapidly decompose BCME. In the present investigation these hot spots were due to too close a contact between the electric resistance heating nest and the outer wall of the reactor.

Both saturated and superheated steam was experimented with. It was found that, in the experimental arrangement used, saturated steam tended to condense too soon so that large droplets of water were formed at the steam inlet in the reactor.

With superheated steam the BCME-scavenging effect was much better. Superheated steam could be easily generated by use of the brass retort.

There was not much visible coalescence of the tiny water droplets which filled the reactor in the form of a whitish fog. Generally speaking, the smaller the primarily formed

droplets are, the more mobile they are and the greater is their surface and their effect in mopping up BCME in air (93).

Condensing water droplets could also be produced by starting with warm air of high relative humidity and then cooling it to under the dew point. This alternative was also tested, but it was found to be unsatisfactory, for the following two reasons: (i) as the air inside the reactor was very pure, it lacked the necessary condensation nuclei, and a considerable undercooling was necessary to make the water vapor condense out of the air, and (ii) the reactor walls were cooler than the inside air, and a relatively large amount of water vapor tended to condense on the inside reactor walls, without first reacting with the BCME present in the air.

Table 21 shows the slow decay of BCME in air at about 30°C and the quick mopping-up of the BCME residue when superheated steam was injected.

Results. It was shown that water vapor in the moment of condensation, ie, in the moment of the aggregation state change, was an effective scavenging agent for BCME in air.

Injections of steam into a space containing BCME vapors in air proved to be more effective than cooling the air to under the dew point, with the attendant separation of liquid water in droplet form from the air.

Superheated steam was found to be more effective than saturated steam.

A discontinuous injection of steam accompanied by rapid air movement was found to be more effective than an injection of the same amount of steam in a single dose, without increasing the rate of air movement.

When the steam contained small amounts of ammonia or of an ammonium salt, its effectiveness in mopping up BCME in air was enhanced.

Furthermore, it was found that BCME is destroyed when the BCME-containing air is made to impinge against a heated surface.

Discussion. The presented findings are of importance for those operations in which BCME is or might be formed.

With the use of injections of (preferably slightly alkalized) steam into the reactor headspaces, BCME can be liquidated before the reactors are opened and their contents can communicate with the outer atmosphere.

Table 21. Comparison of the long-term decomposition rate in dry air with the mopping-up rate of bis(chloromethyl)-ether (BCME) by means of a superheated steam injection.^a

Experiment stage	Reaction time (min)	Concentration of BCME (ppm)	BCME residue (% of input)	Temperature (°C)
Before steam injection	0	2.0	100	34
	7	0.70	35	34
	124	0.64	32	28
	997	0.28	14	21
After steam injection	0	0.28	100	21
	2	0.18	64	25
	8	0.11	39	24
	12	0.008	3	24

^a At time $t=998$ min, 1 g of superheated steam was injected into the 1.4-l reactor which contained a BCME residue of 0.28 ppm. The best fit for the mopping-up reaction was the following linear equation: $c_{\text{BCME}}(\%)=91.21-7.22t$ (t =time in min).

If BCME escapes from the reactors into the workroom air, suitably designed steam screens can be an efficient means for liquidating this compound.

Any such arrangement must, however, be combined with efficient ventilation. The point is that water droplets with dissolved formaldehyde and hydrochloric acid (originated by BCME decomposition) can reevaporate, and thus these two BCME precursors are released into the air again. Under suitable conditions this phenomenon could lead to a renewed formation of BCME "in the background."

The second mechanism for destroying BCME in air, namely, shock-heating of BCME-containing air, can be made use of in connection with the first mechanism, ie, BCME destruction by means of condensing steam, in order to ensure that all BCME is destroyed.

The hot surfaces against which BCME-containing air is made to impinge can be covered with an alkaline catalyst (eg, silica gel imbued with an alkaline metal hydroxide

and dried) in order to increase the rate of BCME destruction.

In equipment for treating BCME-containing effluent air, use can be made of the cyclone principle in which superheated steam is blown into the air vortex inside a cyclone in order to ensure a good mixing.

In the design of equipment for BCME removal from air, it should be kept in mind that the primary droplets formed from condensing steam ought to be as small as possible in order to obtain as large a water surface as possible.

In view of the importance of BCME destruction methods to the chemical industry, further research is indicated as regards both of the described methods of BCME destruction. Of great practical interest would be the study of suitable catalysts for BCME destruction on, hot (or maybe even cold) surfaces.

Chemical engineering solutions for BCME destruction equipment would not seem to present any special problems.

General discussion and conclusions

Bis(chloromethyl)ether formation from formaldehyde-based resins

The respective research resulted not only in industrially important information, but also in the development of an experimental technique which is applicable, in a wider con-

text, in BCME and other studies.

Simulation experiments according to specially designed programs showed that no measurable amounts of BCME were formed when formaldehyde-based resins of the phenol/formaldehyde, urea/formaldehyde, and melamine/formaldehyde type, which

contain both free formaldehyde and chloride ions, were manufactured, handled, processed, and used.

This finding answers the primary question of the present investigation.

The experimental design specially developed for these experiments can be used for investigations of similar character. The water and oil bath equipment operating with glass vial microreactors has proved to be a simple, efficient, and safe way of studying the potential formation of BCME in and from systems involving formaldehyde and chloride ions.

The development of this laboratory technique can be regarded as a technological spin-off of the present project.

Bis(chloromethyl)ether formation from its precursors in air

The simulation experiments concerning the formation of BCME from formaldehyde vapors and gaseous hydrogen chloride were meant only as a complementary study on the modalities of BCME formation, as well as the chemical and physical behavior of BCME.

The question of how much BCME is, or can be, formed in atmospheres containing known amounts of formaldehyde, hydrogen chloride, and water vapor, at a certain temperature and in a certain space that is characterized by its volume, its surface area and the movement of air contained in it, acquired, however, ever increasing importance during the work on this project, especially in connection with the collected data about the actually measured and reported concentrations of BCME in the atmosphere of industrial workplaces.

In the course of experimental work on the present project it was gradually realized that the question of how much BCME formation in air can be expected was a pivotal problem of industrial hygiene which would require further research beyond the scope of the present research project.

Occurrence of bis(chloromethyl)ether, actual and potential concentrations

The actual BCME concentrations that have been measured under industrial operational conditions in workroom atmospheres in the

past have varied between about 0.1 ppb and 10 ppb in air.

There were, however, only a few cases in the literature in which explicit data of measured concentrations of BCME were reported (67, 92, 95, 125, 371, 372). Other reports were positive as to the formation of BCME but less explicit as regards the concentrations found (34, 54, 55, 72, 82, 137, 172, 200, 221, 225, 337, 344, 345, 352, 355, 364, 368, 369, 370, 385), while several reports were negative as regards the possibility of BCME formation in analyzable amounts (generally under 0.1 ppb) from relatively low concentrations of formaldehyde and hydrogen chloride (71, 141, 144, 194, 363, 377).

If the formation of BCME in air were as simple as represented by equation 2 in which the reactants formaldehyde and hydrogen chloride form BCME and water, it would be possible to calculate the equilibrium constant K_1 in the conventional way by means of laboratory experiments with the use of varying concentrations of reactants. The calculated values of the equilibrium constant K_1 as determined at a certain temperature are expected to have only a relatively narrow spread.

Laboratory experiments of this kind with accessible results were made, eg, by Kallos & Solomon in 1973 (144), by Frankel et al in 1974 (92), and for the present investigation in 1979 (see table 8). It is probable that also some other teams made similar experiments for internal use only, without publishing their results.

With the use of equation 2 as a basis, equation 11 could be derived for calculating the equilibrium constant K_1 , namely:

$$K_1 = \frac{(\text{BCME})(\text{H}_2\text{O})}{(\text{HCHO})^2(\text{HCl})^2} \quad (\text{eq 11})$$

After the equilibrium constant K_1 has been determined by experiments, it should be possible to use it in equation 12 for calculating the expected concentration of BCME in the gaseous phase if the concentrations of formaldehyde, hydrogen chloride (or, more generally, chloride ions), and water (eg, in parts per million or in moles per liter) were known.

$$(\text{BCME}) = \frac{K_1(\text{HCHO})^2(\text{HCl})^2}{(\text{H}_2\text{O})} \quad (\text{eq 12})$$

The water term (H_2O) in equation 12 comprises both the reaction water and the water

that forms the atmospheric humidity. As the latter occurs in the 10^4 ppm order of magnitude, it is quantitatively much more important than the actual reaction water when BCME is formed from those precursor concentrations which can actually occur in industrial workrooms.

Calculation of bis(chloromethyl)ether occurrence

When the aforementioned method of calculating the values of K_1 was used, the results were entirely unsatisfactory. Frankel et al's results in table 8 show that the values of the equilibrium "constant" K_1 , calculated on the basis of their experiments, were far from uniform as their extreme values, namely, 2.5×10^{10} and 1.6×10^3 , differ by a factor of 1.6×10^7 . The extreme values of K_1 based on the results of the present investigation differ only by a factor of 10, but even they cannot be used for calculations of the expected BCME concentrations as they are not valid for the same temperature.

While Frankel et al's results are valid for 26°C (299 K) and a relative humidity of the air of 40 %, which yields a concentration of water vapor of 13,300 ppm, the measurements of the present investigation were made at various temperatures and relative humidities because the purpose of these measurements was to discover potential maximum values of BCME concentrations.

The results of Frankel et al's experiments show that the values of K_1 increase systematically and monotonously with decreasing concentrations of the reactants. A similar movement of the values of K_1 could not be detected in the experiments of the present investigation because of the respective differences in experimental design. Thus it can be stated that K_1 is not a constant but a characteristic value that changes with the concentration of the reactants in a seemingly regular and systematic way. A hypothesis has been made that the behavior of the values of K_1 might be due to the surface effect of BCME on the reactor walls.

In a search for a better fit, even the values of K_2 were calculated (see table 8). In these calculations, the atmospheric humidity was regarded as inert matter, and only the amount of water generated in the reaction was considered. This idea was based on observations that BCME/formaldehyde/hydro-

gen chloride/water systems in air sometimes behaved inconsistently. An addition of water in the form of water vapor into the system could decrease the concentration of BCME or keep it constant or even increase it.

It is of course clear that there cannot be two sorts of water and that this procedure is inadmissible from the point of view of reaction kinetics even if the spread of the K_2 values happens to be considerably narrower than that of the K_1 values.

As it is not possible to determine the expected concentration of BCME for a given atmosphere if the value of K_1 calculated at the same temperature for other concentrations of the reactants in another system is known, there are only two possibilities for determining the concentration of BCME for a given system of reactants and reaction conditions: (i) using empirical formulas derived by multiple nonlinear regression of a large amount of experimental data or (ii) relying only on analytical procedures.

Empirical formulas. In chemical engineering, it is often useful to use multiple nonlinear regression procedures for deriving formulas that correlate a certain number of variables in the form of empirical equations showing the dependence of a certain process variable on other process variables or conditions.

The most important operational variables in gaseous systems producing BCME at atmospheric pressure are: (i) the concentration of formaldehyde (HCHO), (ii) the concentration of hydrogen chloride (HCl), (iii) the concentration of water vapor (H_2O), (iv) the reaction temperature T , (v) the volume V of the reaction space, (vi) the area S of the surfaces with which the BCME-containing air comes in contact, and (vii) the average velocity $\bar{v}$ of air currents towards the space-limiting surfaces.

The concentration of BCME is given in parts per billion; the concentrations of formaldehyde, hydrogen chloride, and water are given in parts per million; the reaction temperature is given in Kelvins (absolute temperature); the volume is given in cubic meters; the surface area is given in square meters; and the velocity of air currents is given in meters per second.

It seems that the introduction of an eighth parameter, namely, the dimensionless reactivity index i_r of the environment against BCME might be useful in some cases.

An empirical formula obtained by multiple nonlinear regression and containing the above seven terms would have the following form:

$$(BCME)_{ppb} = A \times (HCHO)_{ppm}^B \times (HCl)_{ppm}^C \times (H_2O)_{ppm}^D \times T_K^E \times V_m^F \times S_m^G \times \bar{V}_{m/s}^H \quad (\text{eq 13})$$

or

$$\log (BCME) = \log A + B \cdot \log (HCHO) + C \cdot \log (HCl) + D \cdot \log (H_2O) + E \cdot \log T + F \cdot \log V + G \cdot \log S + H \cdot \log \bar{V} \quad (\text{eq 14})$$

It is supposed that the separate terms V (in m^3) and S (in m^2) could be replaced by a single term which is their quotient V/S (in m), at least in some cases.

If a sufficient amount of experimental data is available, relatively reliable empirical equations can be calculated for operational use within certain limits even if the respective reaction mechanisms and reaction kinetics are not fully established.

At first sight there seems to be a considerable discrepancy between the actually measured BCME concentrations as found in industrial workplaces (ie, 0.1 to 10 ppb) with tolerable atmospheric concentrations of formaldehyde and hydrogen chloride (with peaks of up to 10 ppm), on one hand, and those concentrations of BCME that were obtained in laboratory simulation experiments in glass reactors of 5- to 10-l volumes, on the other.

So far the most consistent experimental results for deriving a general formula are those of Frankel et al (92). With the use of a multiple nonlinear regression procedure on trivariate data, it was possible to derive the following formula from their experimental results:

$$\log (BCME)_{ppb} = -2.249 + 0.667 \log (HCHO)_{ppm} + 0.774 \log (HCl)_{ppm} \quad (\text{eq 15})$$

The terms (H_2O) , T , V , S , and $\bar{V}$ could not be included as their respective values were constant for all experiments in the set. This formula (with coefficient of determination $r^2=1.00$) is valid for a relative humidity of 40 % and a temperature of 26°C. The reactor size was not given in the original publication, but it can be assumed to have been 5 to 10 l.

If equation 15 is used for calculating the concentrations of BCME in some typical formaldehyde/hydrogen chloride systems, results according to table 22 are obtained.

The values of BCME concentrations presented in table 22 seem rather low if compared with the actually measured BCME concentrations in industry. A probable explanation is that a pronounced wall effect operates in the formation of BCME and that larger reactors would lead to higher BCME concentrations, with the same reactant concentrations, as they better approximate a wall-free space in which the maximum formation of BCME can be expected.

It was actually observed that the formation of BCME is enhanced if the reactor volume increases with constant concentrations of reactants and a constant temperature. Results obtained in the laboratories of a chemical concern, which studied the formation of BCME in 50-l reactors, confirm the hypothesis that the amount of BCME generated from given concentrations of formaldehyde, chloride ions, and water vapor, under constant conditions of temperature and air movement, is greater in large vessels than in small ones. The respective concern forbade however the use of these values in published communications.

An attempt was made to derive an equation which contains the volume term V (in l). By a combination and conversion of selected data from the literature, it was possible to derive the following tentative equation:

$$\log (BCME) = -3.375 + 1.515 \log (HCHO) + 1.377 \log V \quad (\text{eq 16})$$

In this equation the concentration of BCME is given in parts per billion, the concentrations of formaldehyde and hydrogen chloride in parts per million $[(HCHO)=(HCl)]$, and the volume of the reactor in liters. The respective coefficient of determination was $r^2=0.98$.

Owing to the mentioned limitations and to the fact that data from different simulation experiments were coupled and used, equation 16 ought to be considered only as proof of the feasibility for the principle involved.

The idea that a reactivity index i_r of the environment, ie, of the contact surfaces and the gaseous milieu, would be useful is based on the following reasoning:

It is known, and the experiments in the present investigation have confirmed, that different materials sequester and scavenge BCME (probably by adsorption and/or decomposition) with different intensities. Deactivated borosilicate glass is relatively in-

Table 22. Calculated concentrations of BCME, if the general formula derived from Frankel et al's experiments (92) is used.

Concentration of formaldehyde (ppm)	Concentration of hydrogen chloride (ppm)	Concentration of BCME (ppb)
1	1	0.006
1	5	0.02
2	5	0.03
5	5	0.06
10	10	0.16

active against BCME, while, eg, cellulose or materials with a thin water film on their surfaces quickly react with BCME.

If the reactivity index i_r of the environment in which BCME occurs in the gaseous phase in air is expressed by means of the following equation:

$$i_r = \frac{(\text{BCME})_{\text{calc}} - (\text{BCME})_{\text{anal}}}{(\text{BCME})_{\text{calc}}} \quad (\text{eq 17})$$

where $(\text{BCME})_{\text{calc}}$ =concentration of BCME as calculated with the use of equation 13 or 14 and $(\text{BCME})_{\text{anal}}$ =concentration of BCME as determined by analysis, then the extreme values of i_r , ie, 0 and 1, signify the following limiting states: $i_r=0$ when the analytically determined concentration of BCME is equal to the calculated value $[(\text{BCME})_{\text{calc}}=(\text{BCME})_{\text{anal}}]$, which means that the environment liquidates no BCME; $i_r=1$ when no BCME is found analytically, while the calculated concentration of BCME has a definite value $[(\text{BCME})_{\text{anal}}=0; (\text{BCME})_{\text{calc}} \neq 0]$, which means that the environment liquidates all BCME which happens to be released into it and/or formed in it.

An example will show the application of the presented principle. If the respective values are $(\text{BCME})_{\text{calc}}=1.0$ ppm and $(\text{BCME})_{\text{anal}}=0.3$ ppm, then the reactivity index is $i_r=(1.0-0.3)/1.0=0.7$. This means that the environment liquidates (adsorbs and/or decomposes) 70 % of the amount of BCME which is released into and/or formed in the atmosphere of the space in question.

The reactivity index i_r can be a useful indicator for assessing the effectivity of the measures which have been taken to reduce the occurrence of BCME in the air of an enclosed space, ie, of a space confined by and containing such surfaces as interfere with BCME in the enclosed air.

It is, however, necessary to make the following reservation: Provided equation 13 were used indiscriminately, the concentration of BCME would appear to continue growing towards infinity if volume V were allowed to increase beyond measure.

Theoretically, it is true that a really wall-free reactor is the one with infinite volume. But in practice the concentration of BCME is bound to even out towards a true chemical equilibrium in a much smaller volume.

Equation 13 must, therefore, be based on the assumption that BCME in environments with a given concentration of formaldehyde, chloride ions, and water vapor, as well as with a given temperature, is formed with a rate that is proportional to the reaction volume V and, at the same time, is decomposed with a rate that is proportional to the size of the surfaces, their reactivity towards BCME, and the mass transfer factor (in this case, mainly the air movement towards the surfaces).

When volume V continues to grow, the last kinetic component will play an increasingly important role. In small vessels, the mass transport can be rapid with respect to the rates of the chemical reactions that go on in the gas phase and on the surfaces.

After a certain size of volume has been reached, the mass transport can be expected to become the dominant factor. This phenomenon occurs before the volume becomes infinite (eg, in large factory halls), and the concentration of BCME will come near to the true equilibrium for purely gas-phase reactions.

In a diagram in which volume V would form the abscissa and the concentration of BCME the ordinate, equation 13 would show the concentration of BCME tending to grow toward infinity with volume V increasing beyond all measure. But because of the mass transport factor the concentration of

BCME would, in reality, tend to approach only an asymptotic value corresponding to the equilibrium concentration of BCME.

Pioneering work as regards the calculation of BCME concentrations using formulas derived by means of nonlinear multiple regression was done by ten Berge (28 and private communication of 3 July 1981). He also showed the importance of using reaction data that are as complete as possible. When he correlated only the concentrations of formaldehyde and hydrogen chloride, he obtained equations that gave the following results for 2 ppm of formaldehyde and 5 ppm of hydrogen chloride in air: 0.005 ppb of BCME for the results of the present investigation (taken as averages), 0.027 ppb of BCME for the results of Frankel et al (92), and 0.025 ppb of BCME for the results of these two investigations combined. If, on the other hand, the concentration of water vapor is considered and the available experimental data are used, then the results are 1.4 ppb of BCME for 1,000 ppm of water vapor (corresponding to a relative humidity of 4.3 %) and 0.14 ppb of BCME for 10,000 ppm of water vapor (corresponding to a relative humidity of 43 %) at the respective temperature. It can be seen that the latter results are much nearer the actually found concentrations of BCME (0.1 to 10 ppb) than the former.

Ten Berge's work seems to confirm the possibility of deriving a formula of the equation 13 type for calculating the concentration of BCME in the workroom air provided the reactant concentrations and the reaction conditions are known.

In the light of experiences so far gained with BCME simulation experiments, it would seem that the following minimum sets of variables would have to be used in deriving a formula of the equation 13 type for predicting the occurrence of BCME in air: (i) ten combinations of formaldehyde and hydrogen chloride concentrations, (ii) two temperatures, (iii) two relative humidities, and (iv) three reactor sizes. Thus a total of at least 120 separate experiments would be needed and each experiment would have to be repeated at least twice for the sake of accuracy. Besides, a way must be found to vary the mass transport in the experimental reactors in a controllable way which can simulate air currents in industrial workrooms.

Analytical procedures. Instead of laboratory-derived equations, it is possible to use mea-

surements of BCME concentrations in the atmosphere only (eg, in industrial workplaces, inside and outside of chemical plants, in polluted urban atmospheres, etc). Such measurements were made, eg, by Yao & Miller (337).

Although there are reliable analytical methods available for freshly formed and/or collected BCME, it seems that a part of the measurements made in the past resulted in inaccurate or even zero data because coadsorbed water vapor on the adsorbent partly or even wholly decomposed the adsorbed BCME. Hints to this possibility were made as early as in the Burlington report of 1975 (371), and experimental proof was given in 1977 by Berkley et al (29). This disappearance of BCME in the adsorbed state seems to be a peculiarity of BCME, as water-stable organic compounds can be retrieved from the same adsorbents in the original amounts despite the presence of coadsorbed water (138). Analytical methods for BCME developed by several chemical companies for internal use also contained instructions for removing the coadsorbed water by means of a stream of inert gas (50, 69).

Besides, the possible role of a wall effect (adsorption and/or decomposition of BCME on surfaces) was not recognized in the past.

Müller and co-workers (188, 189) took up the problem of a reliable method of BCME collection for gas chromatographic-mass spectroscopic analyses and developed a procedure in which the adsorbed BCME is extracted from the granular adsorbent by means of an inert solvent soon after collection. The BCME solution in this solvent is then used for injection into the gas chromatography-mass spectroscopy equipment. This procedure allows delays of up to several weeks between BCME collection and eventual sample analysis. If, on the other hand, BCME is kept adsorbed on the adsorbent in the presence of coadsorbed water, it can disappear, partly or even totally, in a matter of days, depending on which type of adsorbent is used and how much water vapor in the adsorbed state it contains.

Another development by the same team of scientists concerned a spectrophotometric method of haloether analysis which can be used instead of, or as a check on, the gas chromatographic-mass spectroscopic analyses (211).

Prediction of bis(chloromethyl)ether occurrence

The laboratory simulation technique must be considered to be highly inaccurate and thus inadequate for predicting the probable concentrations of BCME which might be formed from known concentrations of formaldehyde and chloride ions in air under specific reaction conditions. For example, Eisner (67) pointed to the great differences in the experimental results of Kallos & Solomon (144) on one hand and Frankel et al (92) on the other.

It does, however, seem that this problem can be solved if the possibility of a wall effect is considered. This effect depends mainly on the area of the surfaces in contact with BCME-containing atmosphere in a given volume, on the reactivity of these surfaces against BCME, and on the mass transfer factor.

The experimental results so far obtained point to the existence of a wall effect (surface effect), but final confirmation must be made by specially designed experiments.

Preventive measures

From the industrial point of view there are two separate aspects of the BCME problem, namely, the release of BCME from reactions in which BCME or CMME is used as a reactant and the formation of BCME from its precursors, either in industrial processes with subsequent release into the workroom air or directly in the workroom air. As regards the former, the resources of modern chemical engineering enable the respective equipment and reactions to be designed in such a way as to present practically no risk of workers being exposed to BCME. This situation is achieved by remote control and complete automation of the processes in question (123, 238).

The second aspect is of considerable hygienic importance, and the results obtained in the present investigation can be summed up as follows: BCME can be easily destroyed by condensing water vapor, especially if this water vapor has an alkaline reaction.

Simulation experiments concerning the drying and curing of formaldehyde-based resins did not show any BCME development, and it is supposed that this fact is due to the

condensation of water vapor released by the drying or curing process.

If BCME is really decomposed by water in the form of tiny fog droplets with a large total surface, then its precursors formaldehyde and hydrogen chloride, are dissolved in the water of these droplets. If these droplets evaporate, then formaldehyde and hydrogen chloride can reenter the atmosphere in gaseous form and there combine to reform BCME "in the background."

There seems to be a possibility that, under certain conditions, an enhanced formation of BCME can occur in a pocket of the atmosphere. This phenomenon is then followed by diffusion of the formed and relatively stable gaseous BCME into the neighboring air masses. Therefore, care must be taken to remove the formaldehyde and hydrogen chloride by ventilation from the workroom air.

It is preferable to prevent the possibilities of BCME formation a priori. This prevention can be achieved with the following measures: (i) a strict spacial and temporal separation of the storing, handling and use of formaldehyde and chemicals which form and/or release formaldehyde, on one hand, and of hydrochloric acid and chemicals which form and/or release chloride ions, on the other; (ii) avoidance of the use of chemicals which – when interacting – can form BCME in the chemical processes; and (iii) design of storing, handling, and manufacturing equipment so as not to allow a leakage of these chemicals into the storerooms and workrooms when the use of chemicals that form BCME cannot be avoided.

Bis(chloromethyl)ether monitoring

As there is great uncertainty as to which concentrations of BCME can be formed from given concentrations of precursors under specific reaction conditions, it is recommended to run two projects simultaneously, ie, a laboratory simulation project in order to establish a workable formula of the equation 13 type and a campaign of BCME analysis in all industrial and nonindustrial environments where BCME is suspected to occur.

If, in the second project not only the concentrations of BCME, but also those of the remaining reactants (ie, formaldehyde and chloride ions) are measured, and if, besides, the temperature and the relative humidity of

the air, as well as the volume of the workroom in question, the area of the surfaces, and the velocity of the air currents are determined, in each case, then a large body of data can be built-up which not only serves as a corrective for the first project but also yields information about the BCME mopping-up characteristics of various environments. The final result will be a refined and reliable formula of the equation 13 type which might make BCME measurements unnecessary in many cases.

While the sample collection in the field must be done locally, the analyses of the collected samples ought to be performed in a centralized way by regional or even national laboratories. There are weighty reasons for this centralization: (i) local laboratories are not usually equipped to deal with this sort of work; (ii) the analyses of BCME are very exacting, and costly sophisticated equipment, such as gas chromatography-mass spectroscopy setups are needed; (iii) the analytical instruments must be maintained in top trim and attended to by skilled and experienced personnel; and (iv) the actual analyses require constant calibrations with pure BCME and BCME solutions. These again need expert handling by competent personnel. – Besides, as few people as possible should be allowed to be in prolonged and regular contact with BCME as a reagent.

Cancer risk due to bis(chloromethyl)ether exposure

So far, most cancer deaths attributed to BCME or CMME have been due to exposures under industrial or laboratory conditions when these substances were used as industrial chemicals or reagents.

The total number of cancer deaths (a majority of them oat-cell bronchial carcinomas) approaches that of vinyl chloride monomer. In 1981, the total number of BCME-caused lung cancer deaths exceeded 70 when Norpoth (209) called attention to 12 newly discovered lung carcinoma cases in the Federal Republic of Germany, noting that from a total of 20 carcinoma cases in that country 12 were due to direct exposure to BCME, while eight occurred in workers engaged in chloromethylation reactions in which BCME precursors were used.

So far, the principal epidemiologic studies have been made in the United States. At

present, a large epidemiologic study is in progress there; it will cover seven major CMME and BCME producers for the period 1948–1979. An estimated 2,000 exposed and 3,500 nonexposed workers will be available for this study, which is expected to be ready for publication in 1982 (224).

No study has been published regarding the danger of BCME formation from formaldehyde and chloride ions in air in terms of cancer cases.

In the Montedison plant of Castellanza (Varese) in Italy, an epidemiologic study is being made at present. It includes both CMME as a reagent and formaldehyde with chloride ions in air. The number of workers employed in the plant since 1946 has been around 2,500, and thus it is possible that relevant data will be obtained even for BCME formed from its precursors in the workroom air (275). The results of this study will probably indicate whether similar epidemiologic investigations ought to be made in other plants where workers have been exposed to a combination of formaldehyde and chloride ions in air.

When workers in whom BCME-caused carcinomas later developed were exposed to BCME or CMME – ie, during the 1940s to 1960s and at the beginning of the 1970s – no measurements were made of BCME or CMME concentrations in the workroom air. Thus only a guess can be made of how high these concentrations might have been. It can be conjectured that the concentrations of CMME might have been from 1 to 10 ppm in the workroom air. Higher concentrations would have been very unpleasant and hardly tolerable. If it is supposed that the carcinogenic agent in technical grade CMME was BCME, the content of which was 1 to 8 %, then the workroom concentration of BCME in air might have varied from 10 to 800 ppb, more probably from 10 to 100 ppb, because the aforementioned concentration of 10 ppm of CMME is supposed to have occurred only in short-term peaks (287, 288, 289, 290).

In the work done by Kuschner et al (152) and reported in 1975, BCME was shown to be potently carcinogenic in rats, both in life-long exposure (6 h/d, 5 d/week) and in limited-time exposures for 10 to 100 d, at a concentration of 0.1 ppm (100 ppb) in air.

As also reported in 1975, Leong et al (159) repeated the experiments on rats under the

same conditions, exposing them to 100, 10, and 1 ppb of BCME, respectively. While the concentration of 100 ppb was again found to be strongly carcinogenic, there were no indications of tumors in the 10 and 1 ppb exposure groups. Thus it might have been concluded that the concentration of 1 ppb of BCME in air represented an acceptable risk, being two orders of magnitude below the concentration of BCME which caused cancer in animals.

The fact that the animal exposure in Leong et al's investigation was not life-long but lasted only six months makes their results incomparable with Kuschner et al's. The consequence is that, so far, nothing is known about the relative health risks associated with the 10- and 1-ppb levels of BCME in air.

What is urgently needed are new life-long animal inhalation experiments at BCME concentrations of 10, 1, and, possibly also, 0.1 ppb of BCME in air.

In the investigations made by Nelson et al and reported in November 1979 (385), rats were exposed to a mixture of 10.6 ppm of hydrogen chloride and 14.6 ppm of formaldehyde in air. This mixture, in which 0.1 ppb of BCME was found, proved to be carcinogenic in rats (87, 255).

If only a small part of the tumors in question (a 25 % incidence of squamous-cell carcinomas of the nasal cavity in rats over a course of 2 a) was caused by the BCME formed in air from formaldehyde and chloride ions, while the rest might have been caused by unreacted BCME precursors, either singly or jointly, then even a BCME concentration as low as 0.1 ppb cannot be considered quite safe.

Regulatory legislation

The present American threshold limit value for BCME, which is accepted in several other countries as well, is 1 ppb in air. This value was announced in the 1979 list published by the American Conference of Governmental Industrial Hygienists (ACGIH) (8). In Sweden, there is no hygienic value for BCME and CMME. These substances are not allowed to be produced or used in industry.

The definition of a threshold limit value (204, 300) is that amount of substance to which nearly all or most workers may be ex-

posed, without personal protective equipment, for 8 h/d, 5 d/week, without predictable injury. Thus a threshold limit value is no property of the substance in question, it is only a "label," a professional guide, established by the ACGIH which, however, is not a government agency. In contrast to the "permissible exposure limit" which is the legally established average concentration of a contaminant to which workers are allowed to be exposed over an 8-h period and which is enforceable by the Federal Government, threshold limit values are not enforceable by law. They are, however, often more restrictive than permissible exposure limits.

It is an interesting fact that BCME, which is a potent carcinogen, has a listed threshold limit value while CMME, which is a much weaker carcinogen (mostly because of its BCME content as impurity), has none. This apparent paradox will be understood if it is realized that BCME can be easily formed from its precursors formaldehyde and chloride ions in air while an atmospheric formation of CMME from its precursors formaldehyde, chloride ions, and methanol has not been proved.

If it is asked why the threshold limit value for BCME is just 1 ppb, there are two possible answers: (i) either the 1-ppb threshold limit value for BCME is a value of convenience because many industrial processes evolve BCME concentrations of 0.1 to 1 ppb in the reactor headspace gases or in the surrounding air and because many workroom atmospheres cannot prevent such BCME concentrations from occurring; or (ii) the 1-ppb threshold limit value for BCME is based on Leong et al's research results of 1975 (159).

As shown in the preceding section, the latest experience is that even a concentration of 0.1 ppb of BCME in air cannot be considered to be totally beyond suspicion of carcinogenicity. Therefore the present threshold limit value of 1 ppb of BCME, which the industry sometimes tends to regard as a license for contaminating the workroom atmospheres with BCME up to this level, stands in an unfavorable relation to the latest experimental results.

It might be argued that – especially because of the sensitivity of BCME to liquid water – there might be a safe concentration threshold (at which all inhaled BCME would be decomposed on the moist mucous membranes of the airways – as suggested by W

Weiss in his private communication of 19 January 1981), but, before such a threshold is safely established, it is probably preferable to presume that it does not exist. Anyway, it is useful to realize that when the BCME concentration in air is as low as 0.1 ppb, then one

breath volume (0.5 l of air) still contains about 1.2×10^{12} molecules of BCME at 25°C. And if the worst-case scenario is imagined, the release of malignancy can be due to a single-event initiation.

References

1. Albert RE, Pasternack BS, Shore RE, Lippmann M, Nelson N, Ferris B. Mortality patterns among workers exposed to chloromethyl ethers: A preliminary report. *Environ health perspect* 11 (1975) 209–214.
2. Albert RE, Pasternack BS, Shore RE, Nelson N. Identification of occupational settings with very high risks of lung cancer. *J natl cancer inst* 63 (1979) 1289–1290.
3. Alderson T. Mechanism of mutagenesis induced by formaldehyde: The essential role of the 6-amino group of adenylic acid (or adenosine) in the mediation of the mutagenic activity of formaldehyde. *Nature* 191 (1961) 251–253.
4. Alderson T. Induction of genetically recombinant chromosomes in the absence of induced mutation. *Nature* 215 (1967) 1281–1283.
5. Allen CFH, Allan JV. Dihalogenated ethers. US patent 2,290,462. 21 July 1942.
6. Althouse R, Tomatis L, Huff J, Wilbourne J. Chemicals and industrial processes associated with cancer in humans: Report of an IARC ad hoc working group on chemicals carcinogenic for humans. International Agency for Research on Cancer, Lyon 1979, pp 26–27.
7. Alvarez M, Rosen RT. Formation and decomposition of bis(chloromethyl)ether in aqueous media. *Int j environ anal chem* 4 (1976) 241–246.
8. American Conference of Governmental Industrial Hygienists. TLVs Threshold limit values for chemical substances and physical agents in the workroom environment with intended changes for 1979. Cincinnati, OH 1979, pp 38–41. (Appendix A, carcinogens).
9. Ames BN. Identifying environmental chemicals causing mutations and cancer. *Science* 204 (1979) 587–593.
10. Ames BN, McCann J, Yamasaki E. Methods for detecting carcinogens and mutagens with the *Salmonella/mammalian* microsome mutagenicity test. *Mutat res* 31 (1975) 347–364.
11. Andersen I, Lundqvist GR, Møhlhave L. Indoor pollution due to chipboard used as a construction material. *Atmos environ* 9 (1975) 1121–1127.
12. Association interprofessionnelle des centres médicaux et sociaux de la région parisienne. Bis-chloromethyl ether $\text{ClH}_2\text{C-O-CH}_2\text{Cl}$. Cahiers de médecine interprofessionnelle, 3e trimestre 1979, no 75 ACMS, Toxicologie PV/1979.
13. Astrup EE, Aomar AM. The molecular structure of bis(chloromethyl)ether, $\text{ClH}_2\text{C-O-CH}_2\text{Cl}$, in the gas phase. *Acta chem scand ser A* 30 (1976) 289–293.
14. Auerbach C. The mutagenic mode of action of formalin. *Science* 110 (1949) 419–420.
15. Auerbach C. History of research on chemical mutagenesis. In: Drake JW, ed. The molecular basis of mutation. Holden-Day, San Francisco, CA 1970, pp 10–11.
16. Auerbach C, Moser H. An analysis of the mutagenic action of formaldehyde food: I Sensitivity of *Drosophila* germ cells. *Z indukt Abstamm Vererbungslehre* 85 (1953) 479–504.
17. Auerbach C, Moser H. Analysis of the mutagenic action of formaldehyde food: II The mutagenic potentialities of the treatment. *Z indukt Abstamm Vererbungslehre* 85 (1953) 547–563.
18. Auerbach C, Moutschen-Dahmen M, Moutschen J. Genetic and cytogenetical effects of formaldehyde and related compounds. *Mutat res* 39 (1977) 317–362.
19. Ault EF, Solomon RA. Apparatus for detection of chloromethyl methyl ether or bis chloromethyl ether. US patent 3,934,981. 27 January 1976.
20. Baba Y, Tanaka T. The gas chromatographic analysis of bis(chloromethyl)ether in air. *Bull chem soc jpn* 51 (1978) 317–318.
21. Bartsch H, Malaveille C, Barbin A, Bresil H, Tomatis L, Montesano R. Mutagenicity and metabolism of vinyl chloride and related compounds. *Environ health perspect* 17 (1976) 193–198.
22. Bartsch H, Montesano R. Mutagenic and carcinogenic effects of vinyl chloride. *Mutat res* 32 (1975) 93–114.
23. Basmadžijeva K, Burkova T, Argirova M, Milanov S, Davidkova E. Biological effect of threshold concentrations of hydrochloric acid and formaldehyde inhaled into the organism. *Khig zdraveopaz* 17 (1974) 480–486.
24. Beavers EM. BCME. *Chem eng news* 52 (1974):29, 3.
25. Beavers EM. Lung cancer in chloromethyl methyl workers. *N eng j med* 290 (1974) 971–972.
26. Beebe GW. Lung cancer in World War I veterans: Possible relation to mustard-gas injury and 1918 influenza epidemic. *J natl cancer inst* 25 (1960) 1231–1252.
27. Belen'kij LI, Karmanova IB, Gol'dfarb JL. Reactions of aromatic and heteroaromatic compounds bearing electron acceptor substituents: XIV Nature of products formed during the reaction of α -acetothienone with α, α' -bis(chloromethyl)ether in the presence of aluminium chloride and reaction mechanisms. *Zh org khim* 9 (1973) 1514–1520.

28. Berge WF ten. Possibility of BCME formation with low precursor concentrations. In: Travenius SZM, ed. Collection of papers: Symposium on bis(chloromethyl)ether (BCME), Copenhagen 1 April 1981. Central library, Perstorp AB, Perstorp, Sweden 1981, pp 42-44.
29. Berkley RE, Pellizzari ED, Bunch JE, Williams RN. Collection of organic vapors from ambient air for instrumental analysis. Paper presented before the Division of Environmental Chemistry of the American Chemical Society, New Orleans, LA, 20-25 March 1977.
30. Bertoni G, Ciccioli P, Severini C, Bruner F. The use of gas-liquid-solid chromatography in environmental and trace analysis. *Chromatographia* 11 (1978):2, 55-58.
31. Bettendorf U. Gewerblich induzierte Lungenkarzinome nach Inhalation alkylierender Verbindungen. *Verh Dtsch Ges Pathol* 60 (1976) 457.
32. Bettendorf U. Gewerblich induzierte Lungenkarzinome nach Inhalation alkylierender Verbindungen (Bischlormethyläther und Monochlormethyläther). *Zentralbl Arbeitsmed Arbeitssch Prophyl* 27 (1977) 140-143.
33. Bettendorf U. Berufsbedingte Lungenkarzinome nach Inhalation alkylierender Verbindungen. *Dtsch med Wochenschr* 102 (1977) 396-398.
34. Bettink JGHD. Nogmaals: Een verradelijke stof: bis(chloormethyl)ether. *Tijdschr soc geneesk* 52 (1974) 586-588.
35. Bille H, Petersen H. Formaldehyd in der Textilausrüstung: Möglichkeiten einer formaldehydfreien oder formaldehydarmen Textilausrüstung. *Melliand Textilber* 57 (1976) 155-165.
36. Black RF, Kurtz CP, Pasek RJ. System for removing chloromethyl ether and bis-chloromethyl ether from air contaminated therewith. US patent 3,980,755. 14 September 1976.
37. Böhme H. Der Einfluss alpha-ständiger Sauerstoff- und Schwefelatome auf die Hydrolysegeschwindigkeit der Kohlenstoff-Halogen-Bindung. *Ber Dtsch chem Ges* 74 (1941) 248-256.
38. Boit H-G. Beilsteins Handbuch der organischen Chemie, Vierte Auflage, System-Nr 75. 1950-1959. Viertes Ergänzungswerk, Erster Band, Fünfter Teil. Acyclische Oxo-Verbindungen $C_nH_{2n}O$. Springer-Verlag, Berlin-Heidelberg-New York 1974, pp 3046-3052.
39. Boucot KR, Weiss W, Seidman H, Carnahan WJ, Cooper DA. The Philadelphia pulmonary neoplasm research project: Basic risk factors of lung cancer in older men. *Am j epidemiol* 95 (1972) 4-16.
40. Boyland E. Biochemistry of occupational cancer. *J soc occup med* 27 (1977):2, 97-101.
41. Boyland E, Sargent S. The local greying of hair in mice treated with X rays and radiomimetic drugs. *Br j cancer* 5 (1951) 433-440.
42. Braswell JR, Spiner DR, Hoffman RK. Adsorption of formaldehyde by various surfaces during gaseous decontamination. *Appl microbiol* 20 (1970) 765-769.
43. Broniarz J, Szymanowski J, Pernak J. Synthesis of hexyl chloromethyl ether. *Chem stosow* 17 (1973) 433-442.
44. Brown SM, Selvin S. Lung cancer in chloromethyl methyl ether workers. *N engl j med* 289 (1973) 693-694.
45. Bruner F, Bertoni G, Severini C. Gas chromatographic determination of bis(chloromethyl)ether emissions in the atmosphere of industrial plants. *Anal chem* 50 (1978) 53-55.
46. Casę RAM, Lea AJ. Mustard gas poisoning, chronic bronchitis, and lung cancer: An investigation into the possibility that poisoning by mustard gas in the 1914-1918 war might be a factor in the production of neoplasia. *Br j prev soc med* 9 (1955) 62-72.
47. Charles SW, Cullen FC, Owen NL. The IR spectrum and molecular conformation of bis-chloromethyl ether. *Spectrochim acta part A* 32 (1976) 1171-1177.
48. Chemical Industry Institute of Toxicology. Statement concerning research findings. Research Triangle Park, NC 1979. (Communication of 8 October 1979).
49. Choudhary G, Cooper CV. Gas chromatography/mass spectrometry: Its application to industrial hygiene analytical problems. *Am ind hyg assoc j* 40 (1976) 39-46.
50. Ciba-Geigy: Die Bestimmung von Bischlormethyläther (BCME) in Luft und Abgasen. Basel 1973. (Bericht aus der Abteilung Analytik, Basel, vom 3. Juli 1973).
51. Collier L. Determination of bis-chloromethyl ether at the ppb level in air samples by high resolution mass spectrometry. *Environ sci technol* 6 (1972) 930-932.
52. Cooper P. Chloromethyl methyl ether in the air. *Food cosmet toxicol* 15 (1977) 244-246.
53. Cooper P. Genetic effects of formaldehyde. *Food cosmet toxicol* 17 (1979) 300-301.
54. Dahlgren CM. Biological decontamination and protection investigation: Project no 2.2.0076. *Toxicol res proj dir* 2 (1977):2, 1-55.
55. Davies DL. BCME: Possible hazard in perspective. *Chem br* 10 (1974) 359.
56. DeFonso LR, Kelton SC. Lung cancer following exposure to chloromethyl methyl ether. *Arch environ health* 31 (1976) 125-130.
57. Demina ND, Vlasova MI, Gusel'nikova VM, Litvinova RE, Kulik EM. Analysis of the reaction products from the synthesis of beta,beta'-dichlorodiethyl ether by gas-liquid chromatography. *Metody anal kontrolya proizvod khim promsti* (1977):5, 12-14.
58. Descudé M. Sur la préparation de l'oxyde de méthyle bichloré symétrique. *Bull soc chim fr* 35 (1906) 953-957.
59. Dingra YR. Removal of bis-chloromethyl ether from chloroacetyl chloride. US patent 4,054,602. 18 October 1977.
60. Dickey FH, Cleland GH, Lotz C. The role of organic peroxides in the induction of mutations. *Proc natl acad sci usa (genetics)* 35 (1949) 581-588.
61. Doorn S. Onderzoek naar de mogelijkheid van de vorming van bischloormethylether voor de AKZO- en MCN-lokatie te Delfzijl. MCN Methanol Chemie Nederland v o f, Delfzijl 1975. (Memo no 75-45 of 9 May 1975).
62. Dow Chemical Company. Werkwijze en inrichting voor het kwantitatief bepalen van de hoeveelheid chloormethylmethylether en bis(chloormethyl)ether in een vloeistof of gas. Dutch patent 7409880. 26 January 1976.
63. Dow Chemical Company. Determination of chloromethyl methyl ether and bis(chloromethyl)ether in fluids. Japanese patent 76/14,394. 4 February 1976.
64. Dow Chemical Company. Analytisches Ver-

- fahren und analytische Vorrichtung. West-German patent 24 33 614. 12 February 1976.
65. Drake J-P. Questions of haloether carcinogenicity. *Food cosmet toxicol* 12 (1974) 551-552.
66. Drew RT, Laskin S, Kuschner M, Nelson N. Inhalation carcinogenicity of alpha halo ethers: I The acute inhalation toxicity of chloromethyl methyl ether and bis(chloromethyl)ether. *Arch environ health* 30 (1975) 61-69.
67. Eisner D. Formation of bis-chloromethylether from hydrogen chloride and formaldehyde. Diamond Shamrock Chemical Co, Nopco Chemical Division, Redwood City, CA 1974. (Ion exchange environmental report no EQR-7412 of 5 September 1974).
68. Ekström G, Ry AB. Planverkets drömnivå för formaldehyd uppfyllt. *Dagens ind* 4 (1979):61, 21.
69. Ellgehausen D. Spurenanalytisches Verfahren zur Bestimmung von bis(chloromethyl)äther in Luft. Sandoz AG, Basel 1973. (Interner Bericht vom 28. Februar 1973).
70. Ellgehausen D. Determination of volatile toxic substances in the air by means of a coupled gas chromatograph-mass spectrometer system. *Anal lett* 8 (1975):1, 11-23.
71. Ellgehausen D. Untersuchung über die Bildung von 1,1'-Dichlordimethyläther bei der Applikation von Kunstharzausrüstungen auf Baumwollgewebe. *Chimia* 30 (1976) 388-389.
72. Ellgehausen D, Robinson T. Formaldehyd und seine Derivate - Ein Beitrag zur Problematik der Toxikologie in der Hochveredlung von Textilien. *Textilveredlung* 13 (1978):1, 25-32.
73. Ember L. The specter of cancer. *Environ sci technol* 9 (1975) 1116-1121.
74. Englesberg E. The mutagenic action of formaldehyde on bacteria. *J bacteriol* 63 (1952) 1-11.
75. Evans JE, Arnold JT. Monitoring organic vapors. *Environ sci technol* 9 (1975) 1134-1138.
76. Evans KP, Mathias A, Mellor N, Silvester R, Williams AE. Detection and estimation of bis(chloromethyl)ether in air by gas chromatography-high resolution mass spectrometry. *Anal chem* 47 (1975) 821-824.
77. Feldman MY. Reactions of nucleic acids and nucleoproteins with formaldehyde. *Prog nucleic acid res mol biol* 13 (1973) 1-48.
78. Feldman MY, Balabanova H, Bachrach U, Pyshnov M. Effect of hydrolyzed formaldehyde-treated RNA on neoplastic and normal human cells. *Cancer res* 37 (1977) 501-506.
79. Figueroa WG, Raszkowski R, Weiss W. Lung cancer in chloromethyl methyl workers. *N engl j med* 288 (1973) 1096-1097.
80. Fishbein L. Formaldehyde and ethylene oxide. In: Hollaender A, ed. *Chemical mutagens - Principles and methods for their detection*. Volume 4. Plenum Press, New York-London 1976, pp 278-280.
81. Fishbein L. Industrial mutagens and potential mutagens: I Halogenated aliphatic derivatives. *Mutat res* 32 (1976) 267-308.
82. Fishbein L. Potential industrial carcinogens and mutagens. Section K. Haloethers. Environmental Protection Agency for the Office of Toxic Substances, Washington DC 1977, pp 96-104 (EPA 560/5-77-005).
83. Fishbein L. Potential halogenated industrial carcinogenic and mutagenic chemicals: III Alkane halides, alkanols, and ethers. *Sci total environ* 11 (1979) 223-257.
84. Fishbein L. Potential carcinogenic and mutagenic industrial chemicals: I Alkylating agents. *J toxicol environ health* 6 (1980) 1133-1177.
85. Fleig I, Thiess AM. Mutagenicity of vinyl chloride: External chromosome studies on persons with and without VC illness, and on VC exposed animals. *J occup med* 20 (1978) 557-560.
86. Fleig I, Thiess AM. Chromosome investigations of persons exposed to dimethylcarbamoyl chloride and diethylcarbamoyl chloride. *J occup med* 20 (1978) 745-746.
87. Formaldehyde Institute. Communication to the European Chemical Industry Ecology and Toxicology Centre (ECETOC) of 19 September 1980. Scarsdale, NY 1980.
88. Formaldehyde Institute. Report on formaldehyde tests. Scarsdale, NY 1980. (Press release of 5 December 1980).
89. Fraenkel-Conrat H, Olcott HS. The reaction of formaldehyde with proteins: V Cross-linking between amino and primary amide or guanidyl groups. *J am chem soc* 70 (1948) 2673-2684.
90. Fraenkel-Conrat H, Olcott HS. Reaction of formaldehyde with proteins: VI Cross-linking of amino groups with phenol, imidazol, or indole groups. *J biol chem* 174 (1948) 827-843.
91. Frankel LS, Black RF. Automatic gas chromatographic monitor for the determination of parts-per-billion levels of bis(chloromethyl)ether. *Anal chem* 48 (1976) 732-737.
92. Frankel LS, McCallum KS, Collier L. Formation of bis(chloromethyl)ether from formaldehyde and hydrogen chloride. *Environ sci technol* 8 (1974) 356-359.
93. Freed VH, Chiou CT, Haque R. Chemodynamics: Transport and behavior of chemicals in the environment. A problem in environmental health. *Environ health perspect* 20 (1977) 55-70.
94. Frenkel K. In vitro chemical and biochemical studies on the interaction of the carcinogenic alkylating agents propane sultone and bis(chloromethyl)ether with DNA and nucleosides. Doctoral thesis, University of New York, New York, NY 1974. (Abstract in *Diss abstr int* B 36 (1976) 5556).
95. Gamble MR. Hazard: Formaldehyde and hypochlorites. *Lab anim* 11 (1977) 61.
96. Gargus JL, Reese WH, Rutter HA. Induction of lung adenomas in newborn mice by bis(chloromethyl)ether. *Toxicol appl pharmacol* 15 (1969) 92-96.
97. Garry VF, Oatman L, Pleus R, Gray D. Formaldehyde in the home: Some environmental disease perspectives. *Minn med* 63 (1980) 107-111.
98. Garschin WG, Schabad LM. Über atypische Wucherungen des Bronchialepithels bei Einführung von Formalin in das Lungengewebe. *Z Krebsforsch* 43 (1935) 137-145.
99. Gevorkyan AA, Badanyan SO, Arakelyan AS. Reactions of haloorganic compounds: Synthesis of tetrahydropyrans by the interaction of allyl halides, bis(chloromethyl)ether and zinc. *Arm khim zh* 27 (1974) 394-400.
100. Gevorkyan AA, Badanyan SO, Kazaryan PI. Cycloalkylation of bis(chloromethyl)ether with 1,3-diene hydrocarbons. *Arm khim zh* 25 (1972) 886-889.
101. Gevorkyan AA, Badanyan SO, Malkhasyan AC,

- Kazaryan PI. Reactions of haloorganic compounds: II Reactions of bis(chloromethyl)ether with allenes and its mechanism. *Arm khim zh* 25 (1972) 587–593.
102. Gevorkyan AA, Badanyan SO, Manukyan AA. Reactions of haloorganic compounds: III Cycloalkylation of bis(chloromethyl)ether by divinylacetylene hydrocarbons. *Arm khim zh* 25 (1972) 623–625.
103. Gevorkyan AA, Badanyan SO, Manukyan AA. Synthesis of 4-chlorotetrahydropyrans by the reaction of bis(chloromethyl)ether with alkyl halides. *Khim geterotsikl soedin* (1973):8, 1143.
104. Gevorkyan AA, Badanyan SO, Manukyan AA, Kazaryan PI. Reaction of bis(chloromethyl)ether with olefins: Synthesis of tetrahydropyrans. *Arm khim zh* 24 (1971) 909–912.
105. Ghora BK. Comparative studies on the lethal and mutagenic effect of formaldehyde and hydrogen peroxide in *Chaetomium aureum* chivers. *Curr sci* 43 (1974) 480–481.
106. Gibney L-Y. Toxic substances control bill draws debate. *Chem eng news* 53 (1975):11, 12–13.
107. Gofmekler VA. Embriotropnoje dejstvije benzola i formal'degida pri ingal'jacionnom puti vozdeystvija v eksperimente. *Gig sanit* (1968):3, 12–16.
108. Gofmekler VA, Puškina NN, Klevцова GN. Nekotoryje biohimičeskiye sdvigi pri izučenii embriotropnogo dejstvija benzola i formal'degida. *Gig sanit* (1968):7, 96–98.
109. Goldschmidt BM, Van Duuren BL, Frenkel K. The reaction of ^{14}C -labelled bis(chloromethyl)ether with DNA. *Proc am assoc cancer res* 16 (1975) 66. (Abstract no 263).
110. Goldsmith JR. Cigarette smoking, lung cancer and CME – A clarification. *J occup med* 23 (1981) 77–78.
111. Goodson R. More on BCME danger. *Chem eng. news* 52 (1974):42, 5.
112. Gorrie TM, Raman SK, Rouette HK, Zollinger H. NMR-investigation of the formaldehyde addition and oligomerisation equilibria in the system formaldehyde/water/acetic acid/hydrochloric acid. *Helv chim acta* 56 (1973):1, 175–195.
113. Gross H, Farkas I, Bognár R. Dichloromethylmethylether als Reagens für die organische Synthese- und Kohlenhydratchemie. *Z Chem* 18 (1978) 201–210.
114. Gwynne P, Whitaker M, Shannon E, Hager M, Begley S. The chemicals around us. *Newsweek* 92 (1978):8, 21–24.
115. Harris WD. BCME danger. *Chem eng news* 52 (1974):48, 3.
116. Haux EH. Langzeitverhalten von Chemikalien wird geklärt. *VDI-Nachr* 33 (1979):30, 2.
117. Heitmann W. Äther, aliphatische. In: Ullmanns Encyklopädie der technischen Chemie, 4. neubearb u erweit Aufl, Band 8. Verlag Chemie, Weinheim/Bergstr 1974, pp 146–157.
118. Hodgman CD, ed. Handbook of chemistry and physics. 44th edition. The Chemical Rubber Publishing Co, Cleveland, OH 1962, pp 982–983.
119. Hoffmann D, Wynder EL. Environmental respiratory carcinogens. In: Searle CE, ed. Chemical carcinogens. American Chemical Society, Washington, DC 1976, pp 324–365. (ACS monograph 173).
120. Holmberg B. Biological aspects of chemical and biological weapons. *Ambio* 4 (1975) 211–215.
121. Horton AW, Tye R, Stemmer KL. Experimental carcinogenesis of the lung: Inhalation of gaseous formaldehyde or an aerosol of coal tar by C3H mice. *J natl cancer inst* 30 (1963) 31–43.
122. Houben-Weyl. Methoden der organischen Chemie. 4. völlig neu gest Aufl, Band V/3 (Halogenverbindungen). Georg Thieme Verlag, Stuttgart 1962, p 841.
123. Hübenett F. Erfahrungen bei der Handhabung toxischer Substanzen in einem emissionsfreien Technikum. Paper presented at the IVSS Colloquium in Frankfurt am Main, 19 June 1979.
124. Hueper WC, Payne WW. Carcinogenic effects of adsorbates of raw and finished water supplies. *Am j clin pathol* 39 (1963) 475–481.
125. Hurwitz MD. Assessing the hazard from BCME in formaldehyde-containing acrylic emulsions. *Am dyest rep* 63 (1974):3, 62–64 & 77.
126. Imperial Chemical Industries Ltd, Agricultural Division, Communication to the European Chemical Industry Ecology and Toxicology Centre (ECETOC) of 28 July 1980. Billingham–Cleveland, 1980.
127. Innes JRM, Ulland BM, Valerio MJ, Petrucelli L, Fishbein L, Hart ER, Pallotta AG, Bates RR, Falk HL, Gart JJ, Klein M, Mitchell I, Peters J. Bioassay of pesticides and industrial chemicals for tumorigenicity in mice: A preliminary note. *J natl cancer inst* 42 (1969) 1101–1114.
128. International Agency for Research on Cancer. IARC monographs on the evaluation of carcinogenic risk of chemicals to man. Volume 4. Lyon 1973, pp 231–238.
129. International Agency for Research on Cancer. IARC monographs on the evaluation of carcinogenic risk of chemicals to man. Volume 4. Lyon 1973, pp 239–245.
130. International Agency for Research on Cancer. IARC monographs on the evaluation of carcinogenic risk of chemicals to man, Volume 9. Lyon 1975, pp 117–123.
131. Iovu M, Cimpeanu G. Tris(ethers): I Condensation of bis(chloromethyl)ether with sodium phenoxide, methylphenoxides, and dimethylphenoxides. *Rev roum chim* 18 (1973) 883–888.
132. Iovu M, Cimpeanu G. Condensarea bis(clorometil)eterului cu clor si brom-fenoxizi de sodiu. *Rev chim (Bucharest)* 27 (1976) 195–197.
133. Iovu M, Cimpeanu G. Triseteri: Condensarea bis(clorometil)eterului cu 4-benzilfenoxizi de sodiu. *Rev chim (Bucharest)* 27 (1976) 373–376.
134. Iovu M, Cimpeanu G, Avramescu F. Policondensarea sarii de sodiu a 4,4'-dihidroxibifenilului cu bis(clorometil)eter: I Policondensarea de echilibru. *Rev chim (Bucharest)* 28 (1977) 723–726.
135. Iovu M, Cimpeanu G, Avramescu F. Policondensarea sarii de sodiu a 4,4'-dihidroxibifenilului cu bis(clorometil)eter: II Policondensarea de neechilibru. *Rev chim (Bucharest)* 28 (1977) 925–927.
136. Iovu M, Cimpeanu G, Miclovici N. Tris(ethers): II Condensation of bis(chloromethyl)ether with sodium cyclohexylphenoxides, methylcyclohexylphenoxides, and chlorocyclohexylphenoxides. *Rev roum chim* 19 (1974) 881–885.
137. Jakobson J. Le symposium de Zurich sur l'ennoblissement textile. *Ind text (Paris)* (1977):1067, 301–302.
138. Janák J, Ružicková J, Novák J. Effect of water vapour in the quantitation of trace components concentrated by frontal gas chromatography on Tenax GC. *J chromatogr* 99 (1974) 689–696.

139. Johncock P, Hewins MAH. Polyfluoroethers from 2,2,3,3,4,4,-hexafluoropentanediol and bis-(chloromethyl)ether and bis(chloromethyl)-substituted aromatic compounds. *J polym sci* 13 (1975) 807-814.
140. Johnson PY, Zitsman J. Reformatsky reaction of ethyl alpha-bromo esters with bis-(chloromethyl)ether. *J org chem* 38 (1973) 2346-2350.
141. Kallos GJ. Exposure to carcinogens. *Chem eng news* 52 (1974):11, 3.
142. Kallos GJ. Method of quantitatively detecting chloromethyl methyl ether and/or bis-chloromethyl ether with improved sensitivity. US patent 4,042,326. 16 August 1977.
143. Kallos GJ, Albe WR, Solomon RA. On-column reaction gas chromatography for determination of chloromethyl methyl ether at one part-per-billion level in ambient air. *Anal chem* 49 (1977) 1817-1820.
144. Kallos GJ, Solomon RA. Investigations of the formation of bis-chloromethylether in simulated hydrogen chloride-formaldehyde atmospheric environments. *Am ind hyg assoc j* 34 (1973) 469-473.
145. Kaplan WD. Formaldehyde as mutagen in *Drosophila*. *Science* 108 (1948) 43.
146. Kavanagh EP, Postgate JR. Absorption and release of hydrocarbons by rubber closures: A source of error in some biological assays. *Lab pract* 19 (1970) 159-160.
147. Khishin AFE. The requirement of adenylic acid for formaldehyde mutagenesis. *Mutat res* 1 (1964) 202-205.
148. Kleopfer RD, Fairless BJ. Characterization of organic components in a municipal water supply. *Environ sci technol* 6 (1972) 1036-1037.
149. Kühn-Birett. Dichlordimethyläther. Merkblätter Gefährliche Arbeitsstoffe, Blatt Nr D 24. Verlag Moderne Industrie, Wolfgang Dummer & Co, München 1974.
150. Kühn-Birett. Dichloräthyläther. Merkblätter Gefährliche Arbeitsstoffe, Blatt Nr D 20, 10. Erg-Lfg 12/79, Merkblatt Nr 1. Verlag Moderne Industrie, Wolfgang Dummer & Co, München 1979.
151. Kuschner M. The causes of lung cancer. *Am rev respir dis* 98 (1968) 573-590.
152. Kuschner M, Laskin S, Drew RT, Cappiello V, Nelson N. Inhalation carcinogenicity of alpha halo ethers: III Lifetime and limited period inhalation studies with bis(chloromethyl)ether at 0.1 ppm. *Arch environ health* 30 (1975) 73-77.
153. Laskin S, Drew RT, Cappiello VP, Kuschner M, Nelson N. Inhalation carcinogenicity of alpha halo ethers: II Chronic inhalation studies with chloromethyl methyl ether. *Arch environ health* 30 (1975) 70-72.
154. Laskin S, Kuschner M, Drew RT, Cappiello VP, Nelson N. Tumors of the respiratory tract induced by inhalation of bis(chloromethyl)ether. *Arch environ health* 23 (1971) 135-136.
155. Lassiter DV. Hazard review of bis(chloromethyl)ether (BCME). US Department of Health, Education, and Welfare, Public Health Service, National Institute for Occupational Safety and Health, Rockville, MD 1973.
156. Lawley PD. Carcinogenesis by alkylating agents. In: Searle CE, ed. *Chemical carcinogens*. American Chemical Society, Washington, DC 1976, pp 83-244. (ACS monograph 173).
157. Lawther PJ, Waller RE. Coal fires, industrial emissions and motor vehicles as sources of environmental carcinogens. *Inserm* 52 (1976) 27-40.
158. Lemen RA, Johnson WM, Wagoner JK, Archer VE, Saccomanno G. Cytologic observations and cancer incidence following exposure to BCME. *Ann n y acad sci* 271 (1976) 71-80.
159. Leong BKJ, Kociba RJ, Jersey GC, Gehring PJ. Effects from repeated inhalation of parts per billion of bis(chloromethyl)ether in rats. *Toxicol appl pharmacol* 33 (1975) 175. (Abstract no 131).
160. Leong BKJ, MacFarland HN, Reese WH. Induction of lung adenomas by chronic inhalation of bis(chloromethyl)ether. *Arch environ health* 22 (1971) 663-666.
161. Leong BKJ, MacFarland HN, Reese WH. Carcinogenicity of methyl ether compounds. *N engl j med* 289 (1973) 378.
162. Li FP, Fraumeni JF, Mantel N, Miller RW. Cancer mortality among chemists. *J natl cancer inst* 43 (1969) 1159-1164.
163. Lloyd OL, Barclay R. Hypothesis. A short latent period for respiratory cancer in a "susceptible" population. *Community med* 1 (1979) 210-220.
164. Loewengart G, Van Duuren BL. Evaluation of chemical flame retardants for carcinogenic potential. *J toxicol environ health* 2 (1977) 539-546.
165. Loewengart G, Van Duuren BL. On the possible formation of bis(chloromethyl)ether from flame retardants. In: Nieburgs HE, ed. *Prevention and detection of cancer*. Part I Volume 2. Marcel Dekker, New York-Basel 1978, pp 1907-1912.
166. Long JR. OSHA pushes ahead on health standards. *Chem eng news* 53 (1975):35, 12-13.
167. Loomis TA. Formaldehyde toxicity. *Arch pathol lab med* 103 (1979) 321-324.
168. Loriot J, Lebbe J, Cavigneaux A, Méry B, Proteau J. Bis-(chloromethyl)-ether et cancer. *Arch mal prof hyg toxicol ind* 37 (1976):10-11, 766-771.
169. Luther M. Beyond Tris: Other chemical finishes called suspect. *Daily news rec* 13 June (1977) 4-5.
170. Makridin VP, Brjuchova EV, Semin GK. Nuclear quadrupole resonance spectra of antimony-121, antimony-123 and chlorine-35 in the antimony pentachloride-bis(chloromethyl)ether complex. *Izv akad nauk sssr khim* (1973):6, 1414-1415.
171. Manolov I, Iovčev A, Karaivanova M. Bis(2-chloroethyl)aminoethyl esters of medium weight and lower fatty acids. *Dokl bolg akad nauk* 31 (1978) 71-72.
172. Marceleno T. Bis-chloromethyl ether in select work environments: Project no 3.1.0212. *Toxicol res proj dir* 2 (1977):3, 1-44.
173. Marceleno T, Bierbaum PJ. A preliminary report on the formation and detection of bis-chloromethyl ether in the industrial and medical environment. US Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, Division of Field Studies and Clinical Investigations, Cincinnati, OH 1974.
174. Marceleno T, Yao CC, Miller GC. Occurrence of bis-chloromethyl ether in textile finishing and possible reaction mechanisms. Paper presented at the American Chemical Society's Annual conference 4-9 April 1976. (Section Paper and Cellulose, no 100).
175. Martin CN, McDermid AC, Garner RC. Testing of known carcinogens and noncarcinogens for their ability to induce unscheduled DNA synthesis in HeLa cells. *Cancer res* 38 (1978) 2621-2627.
176. Maugh TH. Chemical carcinogens: The scientific

- basis for regulation. *Science* 201 (1978) 1200–1205.
177. Maugh TH. Chemical carcinogens: How dangerous are low doses? *Science* 202 (1978) 37–41.
178. McCann J, Ames BN. Detection of carcinogens as mutagens in the Salmonella/microsome test: Assay of 300 chemicals. Discussion. *Proc natl acad sci usa* 73 (1976) 950–954.
179. McCann J, Choi E, Yamasaki E, Ames BN. Detection of carcinogens as mutagens in the Salmonella/microsome test: Assay of 300 chemicals. *Proc natl acad sci usa* 72 (1975) 5135–5139.
180. Méry B. Bis(chlorométhyl)éther et cancer: Thèse pour le doctorat en médecine. Diplôme d'Etat, no 78, Université de Paris VI, Faculté de Médecine, Broussais Hôtel-Dieu, 1975.
181. Meyer J. Dichlordimethyläther: Der Gaskampf und die chemischen Kampfstoffe, 2. Aufl. Verlag von S Hirzel, Leipzig 1926, pp 378–380.
182. Meyer J. Dibromdimethyläther: Der Gaskampf und die chemischen Kampfstoffe, 2. Aufl. Verlag von S Hirzel, Leipzig 1926, pp 380–381.
183. Michailova AA, Lifšic EI, Ivanova LT, Grinberg FS, Temkina RZ, Švarcman GM, Judina GG, Svitkina MM. Ulučćenije sanitarno-gigieničeskikh svojstv drevesnostružebnykh plit. *Gig sanit* (1974):7, 86–88.
184. Montesano R, Tomatis L. Les cancerogènes chimiques. *Lyon méd* 238 (1977):14, 107–117.
185. Morin NC, Kubinski H. Potential toxicity of materials used for home insulation. *Ecotoxicol environ saf* 2 (1978) 133–141.
186. Müller G, Norpoth K. Untersuchungen zur Reaktivität und zum Stoffwechselerhalten halogenierter Äther. In: Norpoth K, ed. Krebsgefährdung am Arbeitsplatz. Arbeitsmedizinisches Kolloquium, Bericht über die 19. Jahrestagung der Deutschen Gesellschaft für Arbeitsmedizin in Münster, 2.–5. Mai 1979. AW Gentner Verlag, Stuttgart 1979, pp 205–211.
187. Müller G, Norpoth K, Eckard R. Identification of S-(carboxymethyl)-L-cysteine and thiodiglycollic acid, urinary metabolites of 2,2'-bis-(chloroethyl)ether in the rat. *Cancer lett* 7 (1979) 299–305.
188. Müller G, Norpoth K, Travenius SZM. Quantitative determination of bis(chloromethyl)ether (BCME) in the ppb range by using portable air sample collectors. *Int arch occup environ health* 48 (1981) 325–329.
189. Müller G, Norpoth K, Zilius Z, Ulyneec U, Travenius SZM. Analysis of BCME in air samples. In: Travenius SZM, ed. Collection of papers: Symposium on bis(chloromethyl)ether (BCME), Copenhagen 1 April 1981. Central library, Perstorp AB, Perstorp, Sweden 1981, pp 19–28.
190. Mukai FH, Hawryluk I. The mutagenicity of some halo-ethers and halo-ketones. Paper presented at the First International Conference, Asilomar. *Mutat res* 21 (1973) 228. (Abstract no 33).
191. Nagornyj PA. Izučćenije kombinirovannogo dejstvija neskol'kich faktorov s pomoščju regressionnogo analiza. *Gig sanit* (1973):7, 76–82.
192. Nagornyj PA. O vrednom dejstvii formal'degida v nizkikh koncentracijach (obzor literatury). *Gig tr prof zabol* (1978):6, 42–44.
193. Nagornyj PA, Sudakova ŽA, Ščablenko SM. K obščetoksicheskomu i allergičeskomu dejstviju formal'degida. *Gig tr prof zabol* (1979):1, 27–30.
194. National Institute for Occupational Safety and Health. NIOSH occupational carcinogenesis program: First year report, July 1, 1975–September 30, 1976. US Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, Rockville, MD 1976, pp 11–15.
195. National Institute for Occupational Safety and Health. Bis(chloromethyl)ether (Bis-CME) in air. In: NIOSH manual of analytical methods. Second edition, Part I NIOSH monitoring methods, Volume 1. Cincinnati, OH 1977, pp 213–1 to 213–5.
196. National Institute for Occupational Safety and Health. Chloromethyl methyl ether (CMME) and bis(chloromethyl)ether (BCME) in air. In: NIOSH manual of analytical methods. Second edition, Part I NIOSH monitoring methods, Volume 1. Cincinnati, OH 1977, pp 220–1 to 220–4.
197. National Institute for Occupational Safety and Health/Environmental Protection Agency. Formaldehyde: Evidence of carcinogenicity. US Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health and US Department of Labor, Occupational Safety and Health Administration, Washington, DC 1980. (Joint NIOSH/EPA current intelligence bulletin 34).
198. Natusch DFS. Potentially carcinogenic species emitted to the atmosphere by fossil-fueled power plants. *Environ health perspect* 22 (1978) 79–90.
199. Nelson N. Carcinogenicity of halo ethers. *N engl j med* 288 (1973) 1123–1124.
200. Nelson N. The chloroethers – Occupational carcinogens: A summary of laboratory and epidemiological studies. *Ann n y acad sci* 271 (1976) 81–90.
201. Nelson N. The carcinogenicity of chloro ethers and related compounds: A brief note. In: Hiatt HH, Watson JD, Winsten JA, ed. Origins of human cancer. Book A, Incidence of cancer in humans. Cold Spring Harbor Laboratory, Cold Spring Harbor, NY 1977, pp 115–118. (Cold Spring Harbor conference on cell proliferation, volume 4).
202. Nelson N. Inhalation carcinogenesis. *Ecotoxicol environ saf* 1 (1977) 289–295.
203. Nelson N, Van Duuren BL, Laskin S, Kuschner M, Albert RE, Pasternack B, Mukai F. Cancer research. *Chem eng news* 53 (1975):40, 5 & 42.
204. Neuman TW, Benashski RC. Toxicology terminology. *Chem eng (NY)* 88 (1981):2, 5 & 7.
205. Nichols RW, Merritt RF. Relative solvolytic reactivities of chloromethyl methyl ether and bis(chloromethyl)ether. *J natl cancer inst* 50 (1973) 1373–1374.
206. Nikolaev AF, Pokonova JV. Poly(imino ethers). USSR patent 254,075. 7 October 1969. (Otkrytiya, izobret, prom obratzysy, tovarnye znaki 46 (1969):31, 89).
207. Nikolaev AF, Polonova JV, Drozdova TG. Stabilizers for rubber. USSR patent 254,761. 17 October 1969. (Otkrytiya, izobret, prom obratzysy, tovarnye znaki 46 (1969):32, 80).
208. Nishioka H. Lethal and mutagenic action of formaldehyde in Hcr⁺ and Hcr[–] strains of *Escherichia coli*. *Mutat res* 17 (1973) 261–265.
209. Norpoth K. Fatal cases of lung carcinoma due to BCME in the Federal Republic of Germany. In: Travenius SZM, ed. Collection of papers: Symposium on bis(chloromethyl)ether (BCME), Copenhagen 1 April 1981. Central library, Perstorp AB, Perstorp, Sweden 1981, pp 29–30.
210. Norpoth K, Müller G. Nachweismöglichkeiten al-

- kylierender Luftinhaltsstoffe. Zentralbl Bakteriol Hyg, 1. Abt, Orig Beiträge 162 (1976) 93–101.
211. Norpeth K, Müller G, Zilius Z, Ulync U, Travenius SZM. Sensitive spectrophotometric determination of carcinogenic alpha chloro ethers. *Int arch occup environ health* 49 (1981) 151–155.
 212. North BF. A review of the potential for the formation of BCME (bis(chloromethyl)ether) in textile finishing. Paper presented at the 1976 International Technical Conference of the American Association of Textile Chemists and Colorists. *Chemical Abstracts (Textiles)* 86 (1977) 86, no 018234.
 213. North BF. Formaldehyde release in textile finishing. *Text chem color* 9 (1977) 223–225.
 214. Novgorodov EN, Chardin AP. Polycondensation of ethylene glycol bis(chloromethyl)ether with diethylene glycol. *Nauch tr volgogr politekh inst* (1967) 625–629.
 215. Novgorodov EN, Slavina LV, Chardin AP. Polycondensation of ethylene glycol bis(chloromethyl)ether with polyhydric alcohols. *Khim khim tekhnol (Volgograd)* (1968) 74–81.
 216. Obe G, Beek B. Mutagenic activity of aldehydes. *Drug alcohol depend* 4 (1979) 91–94.
 217. Oettel H. Toxikologie. In: *Äther, aliphatische. Ullmanns Encyclopädie der technischen Chemie*, 4. neubearb u erw Aufl, Band 8. Verlag Chemie, Weinheim/Bergstr, 1974, pp 155–157.
 218. Olah GA, Beal DA, Olah JA. Aromatic substitution: XXXVIII Chloromethylation of benzene and alkylbenzenes with bis(chloromethyl)ether, 1,4-bis(chloromethoxy)butane, 1-chloro-4-chloromethoxybutane, and formaldehyde derivatives. *J org chem* 41 (1976) 1627–1631.
 219. Olah GA, Yu SH. Protonated chloromethyl alcohol and chloromethyl ethers: Proof for the intermediacy of the elusive chloromethyl alcohol. *J am chem soc* 97 (1975) 2293–2295.
 220. Olin GR. The hazards of a chemical laboratory environment: A study of the mortality in two cohorts of Swedish chemists. *Am ind hyg assoc j* 39 (1978) 557–562.
 221. O'Neill L. Toxicity and pollution problems in the paint industry. *Chem ind (London)* (1976):11, 464–466.
 222. Ottmers DM, Jones DC, Keith LH, Hall RC. Instruments for environmental monitoring. *Chem eng (NY)* 86 (1979):22, 85–96.
 223. Parkes DG, Ganz CR, Polinsky A, Schulze J. A simple gas chromatographic method for the analysis of trace organics in ambient air. *Am ind hyg assoc j* 37 (1976) 165–173.
 224. Pasternack BS. Mortality study of occupational exposure to haloethers. *Dir on-going res cancer epidemiol (NY)* (1980):1091, 10.79.
 225. Pasternack BS, Shore RE, Albert RE. Occupational exposure to chloromethyl ethers. *J occup med* 19 (1977) 741–746.
 226. Perry RS. Use of formaldehyde acceptors to reduce formaldehyde levels on cellulose fabrics. *Abstr pap am chem soc* 179 (1980): abstract no 30.
 227. Poverenny AM, Simonin YA, Saenko AS, Sinzini BI. Possible mechanism of lethal and mutagenic action of formaldehyde. *Mutat res* 27 (1975) 123–126.
 228. Prager B, Jacobson P. Beilsteins Handbuch der organischen Chemie, Vierte Auflage. System-Nr 75. Until 1910.01.01: Erster Band, Monooxo-Verbindungen $C_nH_{2n}O$, c) Kupplungsprodukte des Formaldehydes mit Halogenwasserstoffen. Springer-Verlag, Berlin–Heidelberg–New York 1918, pp 580–583.
 229. Preussmann R, Schneider H, Eppele F. Untersuchungen zum Nachweis alkylrierender Agentien: II Der Nachweis verschiedener Klassen alkylrierender Agentien mit einer Modifikation der Farbreaktion mit 4-(4-Nitrobenzyl)pyridin (NBP). *Arzneim Forsch* 19 (1969) 1059–1073.
 230. Probst H, Schönharting M, Beikirch H. Übertragung von Formaldehyd auf DNA und Desoxynucleotide durch die tumorhemmende N-Mannich-Base N-(Isonicotinamidomethyl)sarkosin. *Hoppe-Seyler's Z physiol Chem* 352 (1971) 1429–1439.
 231. Radding SB, Holt BR, Jones JL, Liu DH, Mill T, Hendry DG. Review of the environmental fate of selected chemicals. Stanford Research Institute, Menlo Park, CA, for the Office of Toxic Substances, US Environmental Protection Agency, Washington, DC 1975, pp 25–28. (Contract no 68-01-2681).
 232. Rall DP. Researching health hazards in the environment. *J am water works assoc* 67 (1975) 447–448.
 233. Ramanathan S, Rivlin J, Stamm OA, Zollinger H. The determination of formaldehyde in cellulose formals and methylated cellulose formals. *Text res j* 38 (1968):1, 63–71.
 234. Randall WS, Solomon SD. Building 6, the tragedy of Bridesburg. Little, Brown & Co, Boston–Toronto 1977.
 235. Rapoport IA. Karbonyl'nyje sojedenenija i chimičeskij mehanizm mutacij. *Dokl akad nauk sssr* 54 (1946) 65–68.
 236. Ratnayake WE. Studies of the relationship between induced crossing-over and mutation in *Drosophila melanogaster*. *Mutat res* 9 (1970) 71–83.
 237. Reeves WA, Perkins RM, Chance LH. Cotton cross-linked at various degrees of fiber swelling. *Text res j* 30 (1960):3, 179–192.
 238. Ress JF. Tight control prevents exposure to bis(chloromethyl)ether. *Occup health saf* (1977):3, 40–43.
 239. Reznik G, Wagner HH, Atay Z. Lung cancer following exposure to bis(chloromethyl)ether: A case report. *J environ pathol toxicol* 1 (1977) 105–111.
 240. Richter F. Beilsteins Handbuch der organischen Chemie. Vierte Auflage, System-Nr 75. 1910–1919: Erstes Ergänzungswerk, Erster Band, Monooxo-Verbindungen $C_nH_{2n}O$, c) Kupplungsprodukte des Formaldehyds mit Halogenwasserstoffen. Springer-Verlag, Berlin–Heidelberg–New York 1928, pp 304–306.
 241. Richter F. Beilsteins Handbuch der organischen Chemie, Vierte Auflage, System-Nr 75. 1920–1929: Zweites Ergänzungswerk, Erster Band, Monooxo-Verbindungen $C_nH_{2n}O$, c) Kupplungsprodukte des Formaldehyds mit Halogenwasserstoffen. Springer-Verlag, Berlin–Heidelberg–New York 1941, pp 645–648.
 242. Richter F. Beilsteins Handbuch der organischen Chemie, Vierte Auflage, System-Nr 75. 1930–1949: Drittes Ergänzungswerk, Erster Band, Dritter Teil, Monooxo-Verbindungen $C_nH_{2n}O$, 5) Kupplungsprodukte aus Formaldehyd und Halogenwasserstoffen. Springer-Verlag, Berlin–Heidelberg–New York 1959, pp 2587–2595.
 243. Rosenkranz HS. Formaldehyde as a possible carcinogen. *Bull environ contam toxicol* 8 (1972) 242–244.
 244. Saccomanno G, Archer VE, Auerbach O, Saun-

- ders RP, Brennan LM. Development of carcinoma of the lung as reflected in exfoliated cells. *Cancer* 33 (1974) 256–270.
245. Saccomanno G, Saunders RP, Ellis H, Archer VE, Wood BG, Beckler PA. Concentration of carcinoma or atypical cells in sputum. *Acta cytol* 7 (1963) 305–310.
246. Sakabe H. Lung cancer due to exposure to bis(chloromethyl)ether. *Ind health* 11 (1973) 145–148.
247. Satish J, Wanner HU. Source et importance de la pollution de l'air à l'intérieur des bâtiments. *Soz Praeventivmed* 21 (1976) 124–125.
248. Sawicki E. Bis(chloromethyl)ether (Bis-CME) in air analytical methods. *Health lab sci* 12 (1975) 403–406.
249. Sawicki E. Analytical method for chloromethyl methyl ether (CMME) and bis-chloromethyl ether (BCME) in air. *Health lab sci* 13 (1976) 78–81.
250. Sawicki E. Chemical composition and potential "genotoxic" aspects of polluted atmospheres. *IARC sci publ* 16 (1977) 127–157.
251. Sawicki E, Sawicki CR. Analysis of alkylating agents: Applications to air pollution. *Ann n y acad sci* 163 (1969) 895–920.
252. Schlegel H. Lungenkrebs bei Monochlorodimethyläther-(CMME)-Arbeitern. *Schweiz med Wochenschr* 104 (1974) 366–367.
253. Schulting FL, Wils ERJ. Interference of 1-chloro-2-propanol in the determination of bis(chloromethyl)ether in air by gas chromatography-mass spectrometry. *Anal chem* 49 (1977) 2365–2366.
254. Segal A, Loewengart G, Sudberg S. A new personal monitoring device for the detection of beta-propiolactone and other alkylating agents. *Arch environ health* 36 (1978):1, 33–35.
255. Sellakumar AR, Albert RE, Rusch GM, Katz GV, Nelson N, Kuschner M. Inhalation carcinogenicity of formaldehyde and hydrogen chloride in rats. *Proc am assoc cancer res* 21 (1980) 106.
256. Semin YA, Kolomyitseva EN, Poverennyi AM. Effects of products of the reaction of formaldehyde and amino acids on nucleotides and DNA. *Mol biol (Engl transl)* 8 (1974) 276–285.
257. Senatskommission der Deutschen Forschungsgemeinschaft zur Prüfung gesundheitsschädlicher Arbeitsstoffe. Gefährliche Arbeitsstoffe: Carcinogene Wirkung von Antimontrioxid und Formaldehyd. *Bundesarbeitsblatt* (1980):3, 68–69.
258. Shabad LM. Development of the concept of chemical carcinogens. *Vest akad med nauk sssr* (1977):10, 11–14.
259. Shadoff LA, Kallos GJ, Woods JS. Determination of bis(chloromethyl)ether in air by gas chromatography-mass spectrometry. *Anal chem* 45 (1973) 2341–2344.
260. Shooter KV. Assays for phosphotriester formation in the reaction of bacteriophage R 17 with a group of alkylating agents. *Chem biol interact* 11 (1975) 575–588.
261. Simonov VV, Ryabchenko NI, Poverennyi AM. Differential spectrophotometric study of melting DNA in presence of formaldehyde. *Mol biol (Engl transl)* 1 (1967) 297–301.
262. Siomin YA, Simonov VV, Poverennyi AM. The reaction of formaldehyde with deoxynucleotides and DNA in the presence of amino acids and lysine-rich histone. *Biochim biophys acta* (1973):331, 27–32.
263. Slaga TJ, Bowden GT, Shapas BG, Boutwell RK. Macromolecular synthesis following a single application of alkylating agents used as initiators of mouse skin tumorigenesis. *Cancer res* 33 (1973) 769–776.
264. Solomon RA. Detection of chloromethyl methyl ether or bis-chloromethyl ether. US patent 3,944,389. 16 March 1976.
265. Solomon RA, Ault EF. Method and apparatus for determining the amount of chloromethyl methyl ether and bis(chloromethyl)ether in a fluid. South African patent 75/1213. 12 December 1975.
266. Solomon RA, Kallos GJ. Determination of chloromethyl methyl ether and bis(chloromethyl)ether in air at the part per billion level by gas-liquid chromatography. *Anal chem* 47 (1975) 955–957.
267. Spirtas R, Kaminski R. Angiosarcoma of the liver in vinyl chloride/polyvinyl chloride workers: 1977 update of the NIOSH register. *J occup med* 20 (1978) 427–429.
268. Standish NW. Communication from the Society of Plastic Industry, Plastic Bottle Institute, Toronto 1974. (Press release of 17 October 1974. Original communication from the Standard Oil Company of 12 September 1974, Section "Other FDA Studies").
269. Stellman JM. Safety caution with BCME. *Chem eng news* 52 (1974):25, 3.
270. Summers L. The alpha-haloalkyl ethers. *Chem rev* 55 (1955) 301–353.
271. Swenberg JA, Kerns WD, Mitchell RI, Gralla EJ, Pavkov KL. Induction of squamous cell carcinomas of the rat nasal cavity by inhalation exposure to formaldehyde vapor. *Cancer res* 40 (1980) 3398–3402.
272. Szymik Z, Podkoscielny W, Rudz W. Polykondensationsprodukt aus 4,4'-bis-chlormethyliertem Diphenylthioäther und dem Natriumsalz der Piperazin-N,N'-bis-Thioldithionsäure. *Angew makromol Chem* 45 (1975) 185–189.
273. Taylor LD, McLaughlin P. Preparations and reactions of quaternary salts of bis(chloromethyl)ether. *J appl polym sci* 20 (1976) 2225–2228.
274. Taylor LD, Simon MS. On the carcinogenicity of bis(chloromethyl)ether and chloromethyl methyl ether. *J phys chem* 78 (1974) 2696.
275. Terracini B. Epidemiological study on workers exposed to chloromethyl methyl ether (CMME) and bis-chloromethyl ether (BCME). *Dir on-going res cancer epidemiol* (NY) (1980):387, 12.79.
276. Tesoro G. The cross-linking of cotton cellulose with quaternary ammonium derivatives of bis-chloromethyl ethers. *Text res j* 30 (1960):3, 192–201.
277. Thiess AM, Hey W, Zeller H. Zur Toxikologie von Dichlorodimethyläther: Verdacht auf kanzerogene Wirkung auch beim Menschen. *Zentralbl Arbeitsmed Arbeitsschutz* 23 (1973):4, 99–102.
278. Thomas DMC. Chloromethyl methyl ether. *Lancet* 2 (1973) 739.
279. Tomatis L, Agthe C, Bartsch H, Huff J, Montesano R, Saracci R, Walker E, Wilbourn J. Evaluation of the carcinogenicity of chemicals: A review of the monographs program of the International Agency for Research on Cancer. *Cancer res* 38 (1978) 877–885.
280. Tosunyan AO, Dangyan FV, Gevorkyan AA. Chemistry of unsaturated compounds: Addition of

- bis(chloromethyl)ether to some unsaturated systems. *Arm khim zh* 25 (1972) 1007–1011.
281. Toth B. A critical review of experiments in chemical carcinogenesis using newborn animals. *Cancer res* 28 (1968) 727–738.
282. Tou JC, Kallos GJ. Study of aqueous HCl and formaldehyde mixtures for formation of bis(chloromethyl)ether. *Am ind hyg assoc j* 35 (1974) 419–422.
283. Tou JC, Kallos GJ. Kinetic study of the stabilities of chloromethyl methyl ether and bis(chloromethyl)ether in humid air. *Anal chem* 46 (1974) 1866–1869.
284. Tou JC, Kallos GJ. Possible formation of bis(chloromethyl)ether from the reaction of formaldehyde and chloride ion. *Anal chem* 48 (1976) 958–963.
285. Tou JC, Westover LB, Sonnabend LF. Kinetic studies of bis(chloromethyl)ether hydrolysis by mass spectrometry. *J phys chem* 78 (1974) 1096–1098.
286. Tou JC, Westover LB, Sonnabend LF. Analysis of a non-crosslinked water-soluble anion exchange resin for the possible presence of parts per billion level of bis(chloromethyl)ether. *Am ind hyg assoc j* 36 (1975) 374–378.
287. Travenius SZM. Bis(chloromethyl)eter som carcinogen i kemisk industri. Paper presented at the 37th congress of the Swedish Medical Society in Stockholm–Älvsjö, 3–6 December 1980. (Abstract published in *Acta soc med suecanae hygiea* 89 (1980):5, 360).
288. Travenius SZM. Resumé of the BCME research in the plastics industry. In: Travenius SZM, ed. Collection of papers: Symposium on bis(chloromethyl)ether (BCME), Copenhagen 1 April 1981. Central library, Perstorp AB, Perstorp, Sweden 1981, pp 11–18.
289. Travenius SZM. Möjligheterna för haloetrar att bildas i industriella processer. *Arbetsarskyddsfonden*, Stockholm 1981. (Arbetsarskyddsfondens rapport no 397).
290. Travenius SZM. BCME-bildning från formaldehyd och klorväte i luft när reaktanterna förekommer i gränsvärdeskoncentrationer. Paper presented at the 38th congress of the Swedish Medical Society in Stockholm–Älvsjö, 2–4 December 1981. (Abstract published in *Acta soc med suecanae hygiea* 90 (1981):5, 403).
291. Travenius SZM, Müller G, Norpoth K. Entstehungsbedingungen des Bis(chloromethyl)äthers BCME aus nicht kanzerogenen Vorstufen. In: Norpoth K, ed. Krebsgefährdung am Arbeitsplatz: Arbeitsmedizinisches Kolloquium, Bericht über die 19. Jahrestagung der Deutschen Gesellschaft für Arbeitsmedizin in Münster 2–5 Mai 1979. AW Gentner Verlag, Stuttgart 1979, pp 303–310.
292. Tschamler H. Über binäre flüssige Mischungen: Mischungswärmen, Volumeffekte und Zustandsdiagramme von Chlorex mit Cyclohexan und Methylcyclohexan. *Monatsh Chem* 79 (1948) 223–232.
293. Tschamler H. Über die Chlorexpunkte von Alkoholen (kurze Mitteilung). *Monatsh Chem* 80 (1949) 431–433.
294. Tschamler H, Krischaj H. Über alpha,alpha'-Dichlordimethyläther: Physikalische Konstanten und Entmischungspunkte mit Kohlenwasserstoffen und Alkoholen (kurze Mitteilung). *Monatsh Chem* 81 (1950) 612–614.
295. Tschamler H, Richter E, Wettig F. Mischungen von primären aliphatischen Alkoholen mit Chlorex und anderen organischen Stoffen (Binäre flüssige Mischungen XII). *Monatsh Chem* 80 (1949) 749–758.
296. Tschamler H, Wettig F, Richter E. Die Mischungen von Chlorex mit n-Oktan und 2,2,4-Trimethylpentan (Binäre flüssige Mischungen XI). *Monatsh Chem* 80 (1949) 572–582.
297. Tschegolja AS, Meshirov MS, Idiatulov RK. Faserstoffe aus Phenolformaldehydharzen. *Lenziger Ber* (1978):45, 22–27.
298. Ulrich HM. Polychloralkyläther bzw deren Pyridinium-Verbindungen. *Handbuch der chemischen Untersuchung der Textilfaserstoffe*. Band IV, Teil 1. Springer-Verlag, Wien 1970, pp 154–159.
299. US Oil Co, Chemical Division, East Providence, RI. BCME. *Text chem color* (1975):6, 15. (Advertisement).
300. Vandergrif EF. Meeting OSHA regulations on toxic exposure. *Chem eng (NY)* 87 (1980):11, 69–73.
301. Van Duuren BL. Carcinogenic epoxides, lactones, and halo-ethers and their mode of action. *Ann n y acad sci* 163 (1969) 633–651.
302. Van Duuren BL. Structural prognostication of carcinogenicity and tumor-enhancing activity in various chemicals. In: Nieburgs HE, ed. *Prevention and detection of cancer: Part I Prevention*. Volume 2. Etiology: Prevention methods. Marcel Dekker, New York–Basel 1978, pp 2071–2084.
303. Van Duuren BL, Goldschmidt BM, Katz C, Langseth L, Mercado G, Sivak A. Alpha-haloethers: A new type of alkylating carcinogen. *Arch environ health* 16 (1968) 472–476.
304. Van Duuren BL, Goldschmidt BM, Katz C, Seidman I. Dimethylcarbamy chloride, a multipotential carcinogen. *J natl cancer inst* 48 (1972) 1539–1541.
305. Van Duuren BL, Goldschmidt BM, Katz C, Seidman I, Paul JS. Carcinogenic activity of alkylating agents. *J natl cancer inst* 53 (1974) 695–700.
306. Van Duuren BL, Goldschmidt BM, Loewengart G, Smith AC, Melchionne S, Seidman I, Roth D. Carcinogenicity of halogenated olefinic and aliphatic hydrocarbons in mice. *J natl cancer inst* 63 (1979) 1433–1439.
307. Van Duuren BL, Goldschmidt BM, Seidman I. Carcinogenic activity of di- and trifunctional alpha-chloro ethers and of 1,4-dichlorobutene-2 in ICR/HA Swiss mice. *Cancer res* 35 (1975) 2553–2557.
308. Van Duuren BL, Katz C, Goldschmidt BM, Frenkel K, Sivak A. Carcinogenicity of halo-ethers: II Structure-activity relationships of analogs of bis(chloromethyl)ether. *J natl cancer inst* 48 (1972) 1431–1439.
309. Van Duuren BL, Laskin S, Goldschmidt BM. Determination of bis(chloromethyl)ether at the ppb level in air samples by high-resolution mass spectroscopy. *Environ sci technol* 7 (1973) 744.
310. Van Duuren BL, Laskin S, Nelson N. Carcinogenicity of alpha-chloro ethers. *Chem eng news* 50 (1972):13, 55 & 62.
311. Van Duuren BL, Sivak A, Goldschmidt BM, Katz C, Melchionne S. Carcinogenicity of halo-ethers. *J natl cancer inst* 43 (1969) 481–486.
312. Ven LGJ van der, Venema A. Determination of bis(chloromethyl)ether in air. *Anal chem* 51 (1979) 1016–1019.

313. Venema A. Determination of bis-(chloromethyl)ether in air. *Anal abstr* 39 (1980) 458 (abstract no 4H27).
314. Wada S, Miyanishi M, Nishimoto Y, Kambe S, Miller RW. Mustard gas as a cause of respiratory neoplasia in man. *Lancet* 1 (1968) 1161–1163.
315. Wagoner JK, Archer VE, Lundin FE, Holaday DA, Lloyd JW. Radiation as the cause of lung cancer among uranium workers. *N engl j med* 273 (1965) 181–188.
316. Walker JF. Reactions of formaldehyde with inorganic agents. Formaldehyde. Third edition. Reinhold Publishing Corp, New York, NY 1964, pp 231–263.
317. Walker JF. Reactions of formaldehyde with aliphatic hydroxy compounds and mercaptans. Formaldehyde. Third edition. Reinhold Publishing Corp, New York, NY 1964, pp 264–284.
318. Wanner HU, Deuber A, Satish J, Meier M, Sommer H. Luftverunreinigung in der Umgebung von Strassen. *Soz Praeventivmed* 21 (1976) 122–123.
319. Watanabe F, Matsunaga T, Soejima T, Iwata Y. Study on the carcinogenicity of aldehydes: First report: Experimentally produced rat sarcomas by repeated injections of aqueous solution of formaldehyde. *Jpn j cancer res* 45 (1954) 451–452.
320. Watanabe F, Sugimoto S. Study on the carcinogenicity of aldehydes: Second report: Seven cases of transplantable sarcomas of rats appearing in the area of repeated subcutaneous injections of urotropin. *Jpn j cancer res* 46 (1955) 365–367.
321. Wegman DH, Peters JM. Oat cell lung cancer in selected occupations: A case-control study. *J occup med* 20 (1978) 793–796.
322. Weisburger JH, Van Duuren BL. Chlormethylmethylether und analoge Verbindungen, eine stark karzinogene Stoffklasse. *Z Chem* 20 (1980) 294.
323. Weiss W. Chloromethyl ethers, cigarettes, cough and cancer. *J occup med* 18 (1976) 194–199.
324. Weiss W. The end-expiratory flow rate in men exposed to chloromethyl ethers. *Am rev respir dis* 113 (1976):4, 83.
325. Weiss W. Respiratory effects of chloromethyl-methyl-ether: Projekt no 3.1.0193. *Toxicol res proj dir* 2 (1977):3, 1–41.
326. Weiss W. The forced end-expiratory flow rate in chloromethyl ether workers. *J occup med* 19 (1977) 611–614.
327. Weiss W. The cigarette factor in lung cancer due to chloromethyl ethers. *J occup med* 22 (1980) 527–529.
328. Weiss W, Boucot KR. The respiratory effects of chloromethyl methyl ether. *J am med assoc* 234 (1975) 1139–1142.
329. Weiss W, Figueroa WG. The characteristics of lung cancer due to chloromethyl ethers. *Am rev resp dis* 113 (1976):4, 84.
330. Weiss W, Figueroa WG. The characteristics of lung cancer due to chloromethyl ethers. *J occup med* 18 (1976) 623–627.
331. Weiss W, Moser RL, Auerbach O. Lung cancer in chloromethyl ether workers. *Am rev resp dis* 120 (1979) 1031–1037.
332. Westover LB, Tou JC, Mark JH. Novel mass spectroscopic sampling device – Hollow fiber probe. *Anal chem* 46 (1974) 568–571.
333. White CG. Collaborative work undertaken by the Office of Population Censuses and Surveys, Medical Statistics Division (III): Projekt no 3.1.0206. *Toxicol res proj dir* 2 (1977):3, 1–43.
334. Wilkins RL, Frankel LS. Analytical monitoring system. US patent 3,807,217. 30 April 1974.
335. Wilkins RJ, McLeod HD. Formaldehyde induced DNA-protein crosslinks in *Escherichia coli*. *Mutat res* 36 (1976) 11–16.
336. Williams FW, Umstead ME. Determination of trace contaminants in air by concentrating on porous polymer beads. *Anal chem* 40 (1968) 2232–2234.
337. Yao CC, Miller GC. Research study on bis(chloromethyl)ether formation and detection in selected work environments. US Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, Division of Surveillance, Hazard Evaluation, and Field Studies, Cincinnati, OH 1979. (DHEW(NIOSH) publication no 79–118).
338. Yao CC, Zollinger H. Exchange of comments: Analytical methods of bis(chloromethyl)ether in air. *Anal chem* 51 (1979) 299–302.
339. Zajdela F, Croisy A, Barbin A, Malaveille C, Tomatis L, Bartsch H. Carcinogenicity of chloroethylene oxide, an ultimate reactive metabolite of vinyl chloride, and bis-(chloromethyl)ether after subcutaneous administration and in initiation-promotion experiments in mice. *Cancer res* 40 (1980) 352–356.
340. Zasuchina GD, Rapoport JA. Izučeniye izmenčivosti virusov kompleksa kleščevogo encefalita pri dejstvii himičeskikh mutagennykh faktorov. *Genetika (Moscow)* 33 (1965):5, 33–37.
341. Zellwolle- und Kunstseide-Ring. Procédé de préparation de nouvelles combinaisons polyhalogénées et de leurs produits de réaction avec des amines tertiaires. French patent 887,113. 26 July 1943.
342. Zitsman J, Johnson PY. Reformatskii reaction of ethyl alpha-bromoisobutyrate and bis-(chloromethyl)ether. *Tetrahedron lett* 44 (1971) 4201–4204.
343. Zochniak A. Product of the polycondensation of bis(chloromethyl)ether with potassium disulfide. *Pr nauk univ slask katowicach* 41 (1973) 165–169.
344. Zollinger H. 12 Jahre Formaldehyd-Forschung: Fallstudie eines Hochschulforschungsprojektes. *Textilveredlung* 12 (1977):1, 3–9.
345. Zollinger H. Formation of bischlorodimethyl ether in textile finishing. *Text chem color* 9 (1977):5, 32/96–33/97.
346. Zudová Z, Landa K. Genetic risk of occupational exposures to haloethers. *Mutat res* 46 (1977) 242–243. (Abstract no 77).
347. —. Dichlormethyl ether. *J ind eng chem* 11 (1919) 827–828.
348. —. Dibromomethyl ether. *J ind eng chem* 11 (1919) 828.
349. —. Exclusive: Chemical suspected in 6 cases of lung cancer. *Occup health saf lett* 2 (1972):6, 1–2.
350. —. 2 groups ask ban on 10 chemicals at workplaces. *New York Times* 31 December (1972) 31.
351. —. Worker exposure to carcinogens assailed. *Chem eng news* 51 (1973):2, 4.
352. —. Concentrates – Science: Bis(chloromethyl)ether can form spontaneously. *Chem eng news* 51 (1973):2, 13.
353. —. Meanwhile, a drive to halt worker exposure to some reportedly carcinogenic chemicals. *Chem eng (NY)* 80 (1973):2, 47.
354. —. Fight shaping up over work rules – OCAW Nader group press for emergency measures in OSHA's proposed controls on alleged car-

- cinogenic chemicals. *Chem week* 112 (1973):6, 41–42.
355. —. Bisklormetyleter kräver uppmärksamhet. *Aktuellt från Arbetarskyddsverket*. March (1973) 1, Stockholm.
356. —. Emergency temporary standard on certain carcinogens. *Fed reg* 38 (1973):85, 10929–10930.
357. —. OSHA issues standards on 14 carcinogens. *Chem eng (NY)* 80 (1973):13, 67.
358. —. Chloräther-Spuren verursachen Krebs. *Frankfurter Allg Ztg* 20 June (1973): (Beilage *Natur und Wissenschaft*, p 1).
359. —. A new chemical carcinogen? *Lancet* 2 (1973) 365–366.
360. —. Top of the news: Carcinogen crackdown. *Chem week* 113 (1973):20, 13.
361. —. Carcinogens. *Fed reg* 39 (1974):20, 3756–3757.
362. —. Final rules set for exposure to carcinogens. *Chem eng news* 52 (1974):6, 12–13.
363. —. An old cancer agent poses a new threat. *Bus week* 31 August (1974) 22.
364. —. Washington newsletter: US safety officials have warned industry of another carcinogen worry. *Chem week* 115 (1974):10, 10.
365. —. A rapid analytical method for monitoring bis-chloromethyl ether. *Chem eng news* 52 (1974):38, 23.
366. —. Concern grows over worker cancer risk. *Chem eng news* 52 (1974):41, 5.
367. —. Rohm & Haas denies suppressing information on the link between cancer and BCME. *Chem eng (NY)* 81 (1974):23, 33–34.
368. —. ATMI reports presence of cancer-producing agent. *Charlotte Observer* 22 February (1975) 12A.
369. —. Textile finishing operations may pose a chemical hazard. *Chem eng news* 53 (1975):9, 19.
370. —. Industry's problems with cancer aired. *Chem eng news* 53 (1975):13, 4.
371. —. Report on NIOSH's preliminary BCME industrial hygiene survey at four Burlington textile finishing facilities in the fall of 1974. US Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, Cincinnati, OH 1975.
372. —. Is finishing-carcinogen hunt a NIOSH paper tiger? *Text world* 125 (1975):4, 23–24.
373. —. NAS panel upholds EPA's pesticides policy. *Chem eng news* 53 (1975):49, 17.
374. —. NIOSH ponders standards for long list of widely used chemicals. *Chem week* 118 (1976):18, 10.
375. —. Toxicologists take cancer testing to task. *Chem week* 118 (1976):22, 31.
376. —. Carcinogenic potential of DMCC. *Am ind hyg assoc j* 37 (1976) 370–371.
377. —. Tests show no formation of the carcinogen bischloromethyl ether in air. *Chem eng news* 54 (1976):32, 20.
378. —. Hazard: Formaldehyde and hypochlorites. *Lab anim* 10 (1976) 357.
379. —. Les apprêts d'ennoblissement face aux problèmes de protection et environnement. *Ind text (Paris)* (1977):1073, 672–674.
380. —. Treat chloroethanes as human carcinogens, NIOSH advises. *Occup health saf lett* 8 (1978):17, 7.
381. —. EPA priority pollutant rules taking shape. *Chem eng news* 56 (1978):39, 41–43.
382. —. Carcinogenic question mark over common chemicals. *New sci* 79 (1978) 920.
383. —. Inhalation of a single large dose of carcinogen said to cause cancer. *Occup health saf lett* 9 (1979):11, 7–8.
384. —. Ur litteraturen. *Kungl Arbetarskyddsstyrelsen*, Stockholm 1979, p 3. (Communication no 2).
385. —. Nelson cites risks in formaldehyde-hydrochloric acid combination. *Occup health saf lett* 9 (1979):22, 2–3.
386. —. Panel to assess formaldehyde health effects. *Nature* 283 (1980) 802.
387. —. Chemical aspects: Formaldehyde, US latest. *Hazards rev* 2 (1980):1, 9.
388. —. Down with formaldehyde! *Pharm j* 225 (1980):6083, 81.
389. —. Toxics list shorter by one. *Chem eng news* 58 (1980):38, 14.

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LANGUAGE

All papers should be submitted in American English, and they should be as concise as possible without detracting from clarity. Articles should be well written, and, if considered necessary, they will be subjected to language correction at the author's risk and expense. *Webster's Third New International Dictionary* should be used as a guide to spelling and word divisions. The recommendations of the International Organization for Standardization (ISO) on measurements [*SI Units and Recommendations for the Use of Their Multiples and of Certain Other Units* (ISO/1000-1973 (E))] should be consulted for accepted measurements and abbreviations, and no article will be accepted for publication which does not follow these recommendations.

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3. Karvonen MJ, Barry AJ, ed. *Physical activity and the heart*. Charles C. Thomas, Springfield, IL 1967.
4. Rautaharju PM, Karvonen MJ. Electrophysiological consequences of the adaptive dilatation of the heart. In: Karvonen MJ, Barry AJ, ed. *Physical activity and the heart*. Charles C Thomas, Springfield, IL 1967, pp 159-183.
5. Secchi GC, Alessio L, Cambiagli G, Andreoletti F. ALA-dehydratase activity of erythrocytes and blood lead levels in "critical" population groups. In: *Proceedings of the interna-*

tional symposium on the environmental aspects of lead, Amsterdam Oct 2-6, 1972. Commission of the European Communities, Luxembourg 1973, pp 595-602.

6. WHO Expert Committee. Environmental and health monitoring in occupational health. World Health Organization, Geneva 1973. (WHO tech rep ser no 535).

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